Neurology

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MARCH--1960
Volume 10 • Number 3

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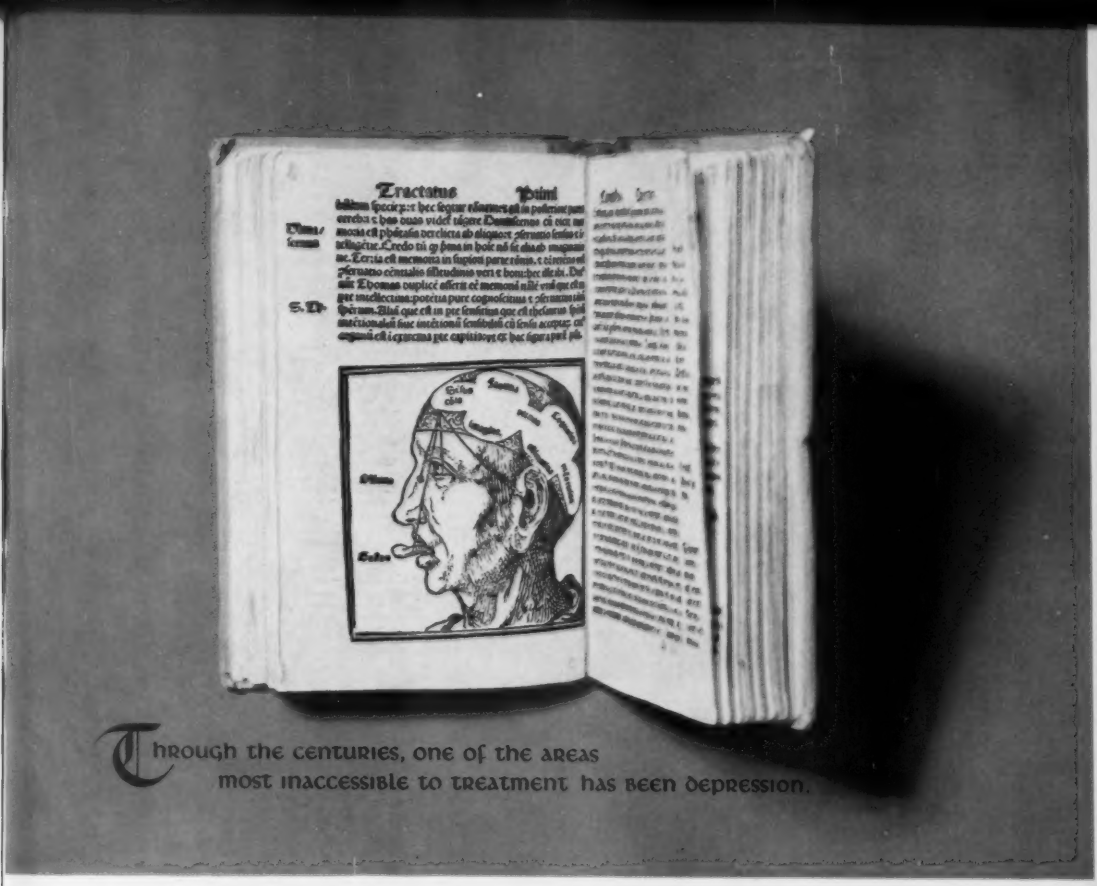

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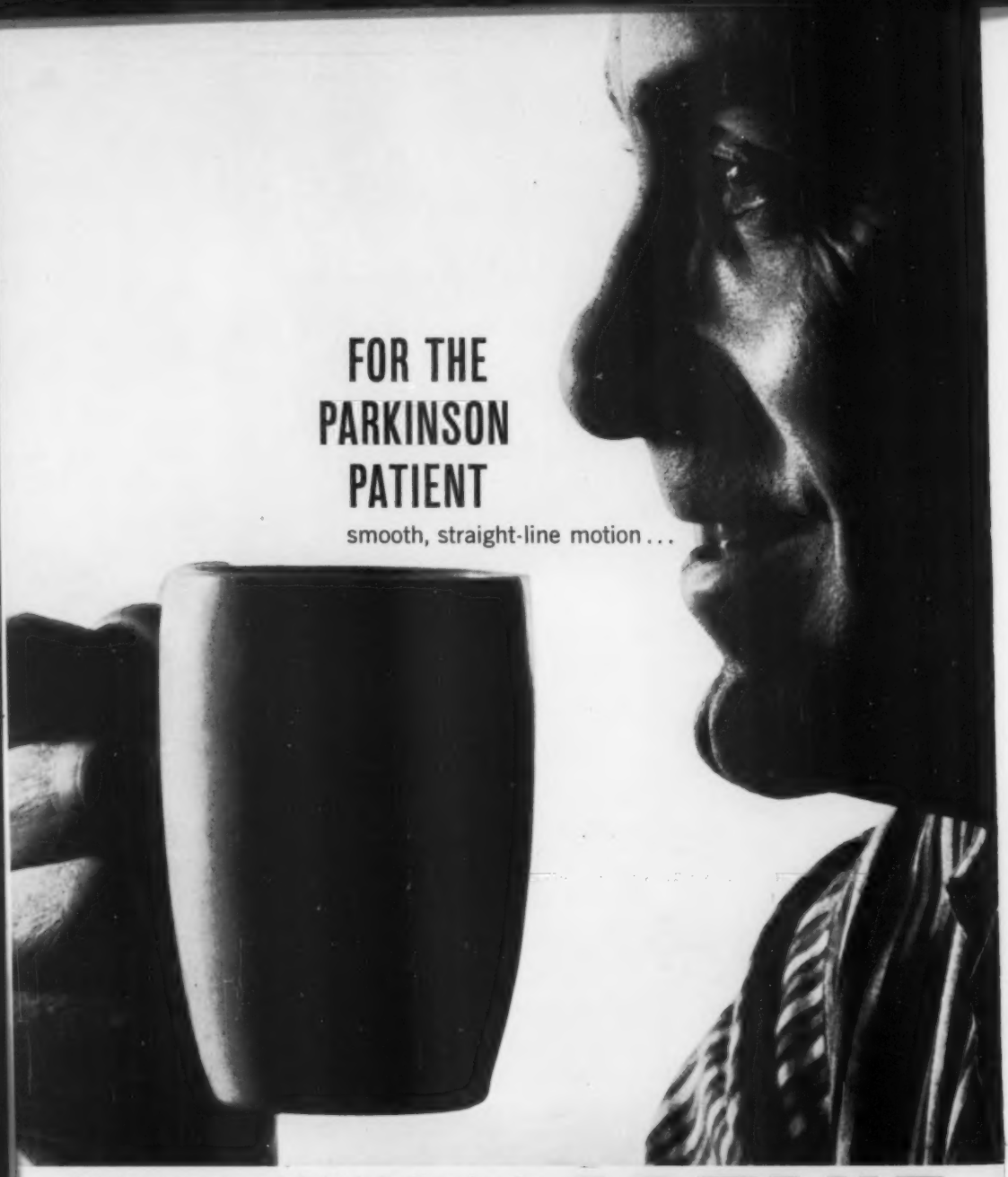

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1. Critchley, M.: British M. J. 2:1214 (Nov. 15) 1958.
2. Doshay, L. J.: Current M. Dig. 22:11 (Nov.) 1956.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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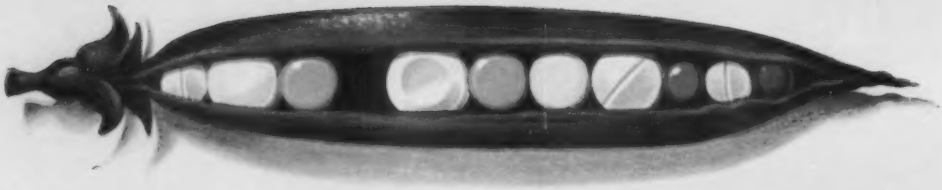

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*Ostfeld, A. M.: Scientific Exhibit. American Academy of General Practice, San Francisco, April 6-9, 1959.

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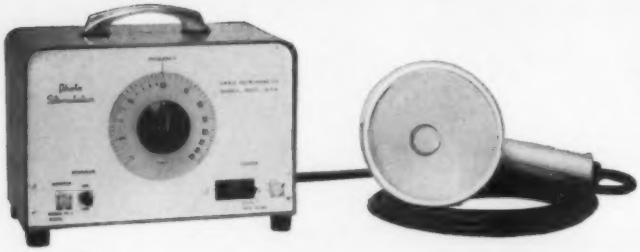

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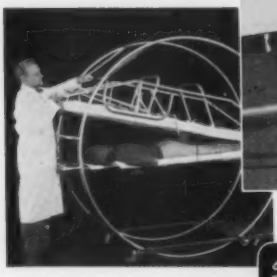

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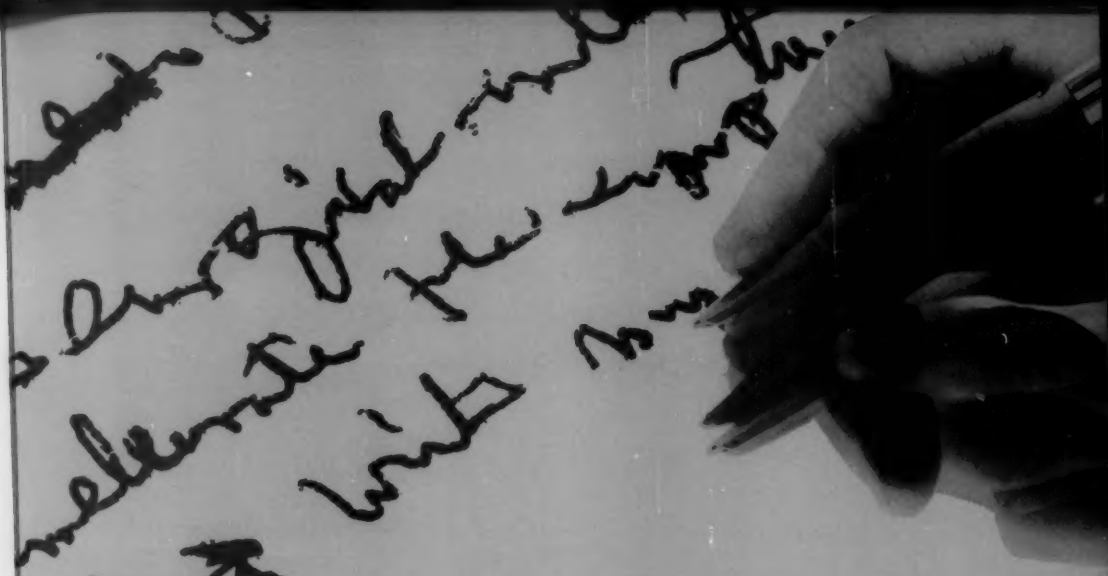

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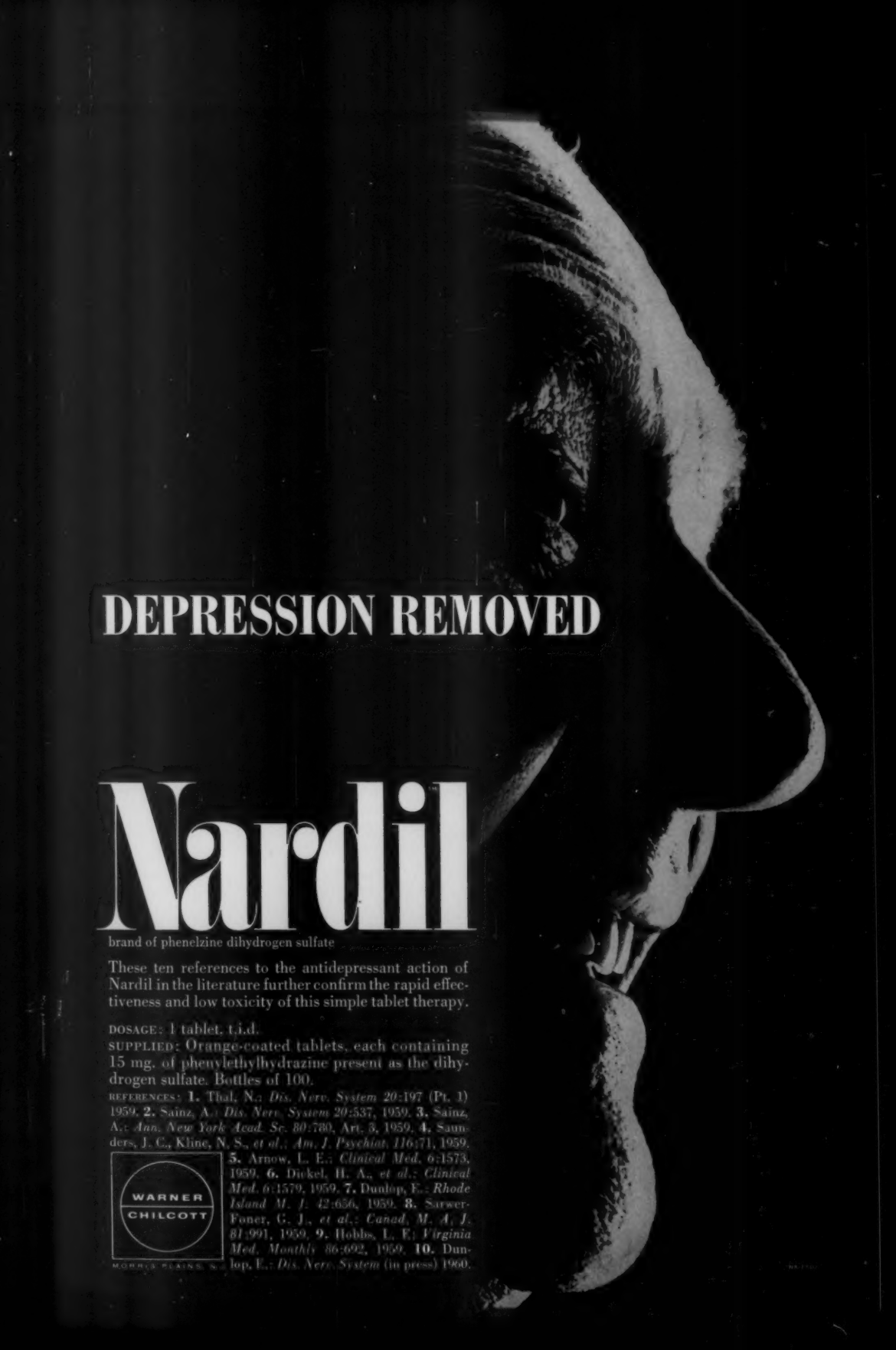

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References: (1) Crawley, J. W.: M. Clin. North America *42:317 (March) 1958. (2) Lennox, W. G., & Cobb, S., cited in Yahraes, H.: Epilepsy—The Ghost Is Out of the Closet, #98, ed. 16, New York, Public Affairs Committee, Inc., 1957.*

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Neurology Volume 10 • Number 3

A comparison of the arrival in the cerebral hemispheres of intravenously injected radioisotope

A preliminary report

W. H. Oldendorf, M.D., P. H. Crandall, M.D.,
R. A. Nordyke, M.D., and A. S. Rose, M.D.

A RADIOISOTOPE technic that appears to furnish useful information concerning human cerebral blood flow has been under preliminary investigation at the Los Angeles Veterans Administration Center. The technic is safe, quite painless, and simple to administer and provides immediate, simultaneous curves representing blood flow in each cerebral hemisphere. This report describes some of our early clinical experiences using this technic.

TECHNIC

The amount of radioiodine-labeled Diodrast in each hemicranium is continuously plotted by 2 collimated detectors for one minute after intravenous injection.

At least two hours before the test, 0.5 cc. of Lugol's concentrated iodine solution is administered orally. This provides a blood level of stable iodine to minimize uptake by the thyroid of any free I^{131} that might be present in the injected test material.

The patient is positioned upright in a chair with an occipital headrest to stabilize the head (Fig. 1); 2 collimated scintillation detector units (sodium iodide crystals) are moved in horizontally so that each collimator centers approximately 3 cm. above the orbit and 4 cm. from the midline. The sensitivity pattern of the 2 collimators is shown in Figure 2. The points on this curve were measured on a line in a plane 8 cm. from the point of contact of the collimators with the forehead. These measurements indicate a rejection of the opposite hemisphere of more than 32 to 1 in favor of the ipsilateral hemisphere measured at about the midpoint of the head in the anterior-posterior direction. This is approximately on the dotted line of Figure 1.

The sensitivity of the units is equalized

From Wadsworth Hospital, Veterans Administration Center, Los Angeles, and the Departments of Medicine and Surgery, University of California Medical Center, Los Angeles.

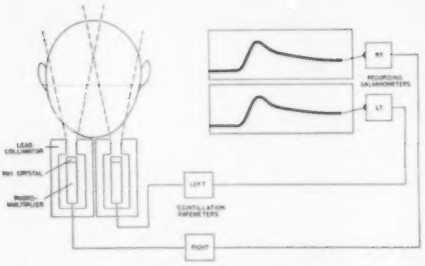

Fig. 1. A diagrammatic scheme of the arrangement of apparatus. The head is shown as seen from above.

using a radioactive standard. In our arrangement, about 250 counts per minute produces full-scale galvanometer displacement. The rate meter time constant is one second, allowing faithful following of count changes without introducing excessive irregularity of the curve due to the randomicity of the scintillations.

A blood pressure cuff (the type with metal ribs) is placed loosely about the right arm. The systolic and diastolic pressures are determined. The cuff is inflated to 10 mm. below diastolic for one minute to obtain full venous distention of the distal arm. A dose of I^{131}-labeled Diodrast is prepared to give 6 μc. per kilogram of body weight in about 2 cc. of solution. Venipuncture with a 21-gauge needle is performed in the antecubital fossa. The sphygmomanometer pressure is raised above systolic and the solution injected. The tubing of the cuff is disconnected to allow it to deflate rapidly. As it deflates, the paper drive on the galvanometer is started and the needle removed. The cuff is immediately removed from the arm to allow free venous drainage.

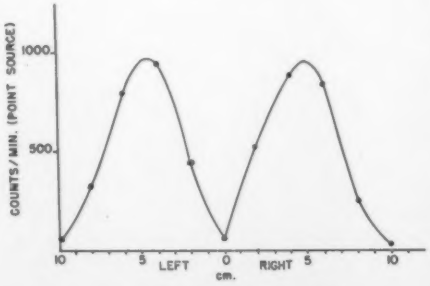

Fig. 2. The sensitivity pattern of the 2 collimated detector units as measured approximately on the dotted line of Figure 1

The tracing is run for sixty seconds. The patient is unaware of any sensation other than the pressure of the sphygomanometer and the venipuncture. An accidental extravasation of radioisotope constitutes no real hazard, since it will be absorbed within a few minutes into the systemic circulation and excreted in the urine. Such an injection would, of course, be useless for our testing purposes.

It is quite possible that some other injection technic might produce a more sharply defined bolus.

Normally, no deflection occurs for the first ten to twenty seconds after cuff release. Some of our curves have shown an early transient rise that is probably due to the passage of the injected bolus into the axilla and thorax near the detector heads. After this initial period, the curves rise sharply as the radioisotope arrives in the cerebrum. Most of this initial rise is probably due to intracranial blood flow, and, after several seconds, some contamination from external carotid circulation undoubtedly occurs.

The curves peak five to ten seconds after they start to rise, then drop off rapidly for several seconds. At about this point, some recirculation of radioisotope appears in the arterial blood and the curve levels off. The test is then complete. Virtually all of the injected material is in the urinary bladder in one hour. The patient is advised to void in one hour to minimize any possible radiation effect.

The technic described here is a result of a pilot study made by simple adaptation to the head of equipment intended for renal output studies. It is not ideally collimated or shielded for our purpose. This results in a contamination by room radiation of the curves intended to monitor only radiation coming through the collimator openings.

Because we are interested in the radioactivity of the test material for only one minute after injection, it can be given in a rapidly excreted form such as Diodrast. If the patient completely empties his urinary bladder one hour after administration, only about a 10 milliroentgen equivalent total body radiation results. This is about one-two-hundredth of the radiation from a similar dose of I^{131}-labeled

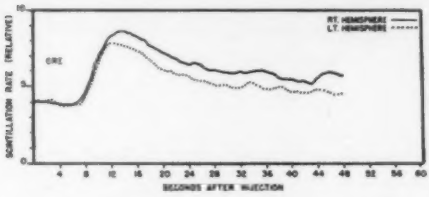

Fig. 3. Curves obtained on a normal male 28 years old

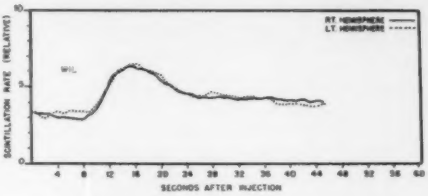

Fig. 4. Curves obtained on a normal male 37 years old

weekly radiation dose. The bladder wall and kidney dosage is less than 0.2 r. Because of these factors, the test could be frequently repeated. The amount of Diodrast injected is so small that allergic sensitivity testing is unnecessary.

CASE MATERIAL AND TEST RESULTS

A total of 13 tests have been performed on 11 patients. Some results are reported here.

Of the 11 patients, 5 were considered to have normal cerebral circulation on clinical grounds. The other 6 had angiographic or autopsy verification of disease with presumed altered circulation in 1 cerebral hemisphere relative to the other. These latter cases consisted of 3 cases of internal carotid occlusion or stenosis, 1 of arteriovenous malformation, 1 of large intracerebral aneurysm, and 1 of intracerebral hematoma adjacent to a metastasis.

Of the normals, 1 was studied with 1 common carotid digitally occluded during the test.

Figures 3 and 4 (GRE, WIL). These are representative normal curves on 28- and 37-year-old males.

Figure 5 (HUR). This 49-year-old normal male had his right common carotid artery digitally compressed during the entire tracing. The right side shows a lower peak delayed several seconds after the left. In this instance, the radioisotope being registered has come through anastomotic channels and has arrived later than the unoccluded side. The failure to drop off rapidly after peaking is probably related to slowing of circulation in the right hemisphere.

Figure 6 (BOD). This 61-year-old male had a sudden right hemiplegia and aphasia three months before radioisotope testing. Arteriography showed total nonfilling of the left internal carotid artery from its origin. In this case and in 2 cases of arteriographically verified internal carotid stenosis, there is a lower, flattened peak on the involved side.

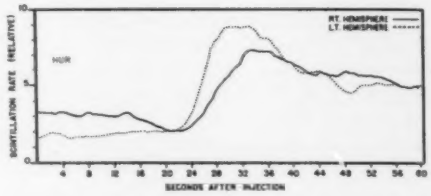

Fig. 5. Curves obtained on a normal male whose right common carotid was digitally compressed during the entire tracing

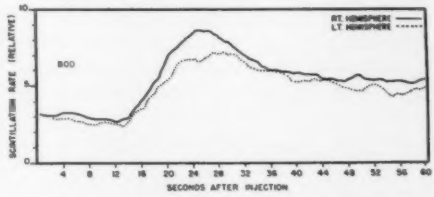

Fig. 6. Curves obtained on a 61-year-old male with left internal carotid occlusion

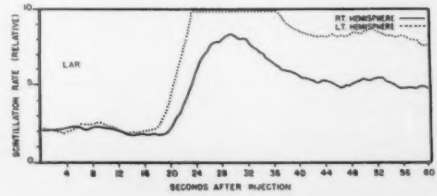

Fig. 7. Curves obtained on a 60-year-old male with a large left frontoparietal arteriovenous malformation

Figure 7 (LAR). This 60-year-old male has

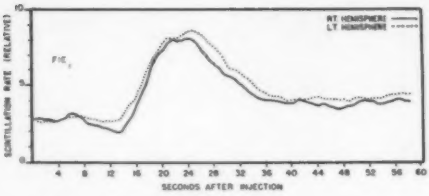

Fig. 8. Curves obtained on a 64-year-old male with early papilledema but no lateralizing clinical findings

an angiographically verified, large, left frontoparietal arteriovenous malformation. A loud left eyeball bruit is present, suggesting an increased internal carotid blood flow on the left.

The radioisotope arrival curve shows a marked rise on the left, striking the limit of the galvanometer range about five seconds after starting to rise. The right curve is probably normal. The very high peak on the left is due to the arrival in the left hemisphere of a large portion of the bolus leaving the left heart. Presumably, this reflects the increased blood flow through the malformation.

Figures 8 and 9. (FIE). This 64-year-old male was discovered to have a left hilar mass in the lung one month before Figure 8 was obtained. At the time of this test, there were no definite lateralizing clinical findings but minimal papilledema was present. Figure 9 was obtained nineteen days after Figure 8. Four days before Figure 9, the patient developed a sudden left hemiplegia, became quite unresponsive, and was noted to have a definite increase in the papilledema on the right. He died twelve days after Figure 9 was obtained.

At autopsy, a metastatic tumor measuring

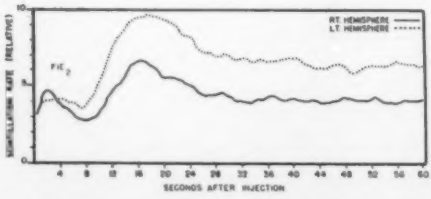

Fig. 9. Same patient as in Figure 8 nineteen days later, after development of sudden left hemiplegia from intracerebral hemorrhage in the right midhemisphere

2 x 3 x 3 cm. was noted, apparently originating in the corpus collosum to the right of the midline. In the rolandic area superior and adjacent to this lesion was a 3-cm. intracerebral hematoma with flattening of the overlying cortex. This was the probable cause of his sudden downhill course starting sixteen days before death.

The change in the 2 examinations with a subsequent low curve on the right side probably reflects a reduced circulation due to the hematoma and other pathologic changes in the right hemisphere.

The results in these cases suggest that the injected test material remains enough of a bolus after passing through the right heart, lungs, left heart, and major arteries to the brain to be clinically useful in plotting its arrival in the head. The results also indicate that a considerable blood flow differential between the hemispheres may be detected by this method.

DISCUSSION

The rate of blood flow regionally in the brain has been little used diagnostically because the multiple exposure angiographic apparatus needed is complicated, expensive, and difficult to use. As a consequence, a few exposures are usually made and vessel position is relied upon. Here, the high spatial resolution allows precise vessel localization. Much more information can be added when multiple exposures are made, allowing determination of time of filling and emptying of the brain.[1] From analysis of such film series, it is evident that there are variable regional and general filling rates in many vascular and neoplastic diseases and possibly in others.

With this in mind, it was felt that a technic that had poor resolution in an optical sense but could differentiate one cerebral hemisphere from the other might still be useful if it clearly defined the passage through the hemispheres of a bolus arriving in the arterial blood. It might then compare the filling and emptying of one hemisphere with the other, although giving no precise structural detail about either. The radioisotope test described here is of value based on this reasoning.

Radioisotopes have been widely used in estimating circulation in various regions. Sev-

eral of these are related to the technic described here. Prinzmetal and associates[2] described the concentration curve of radioisotope in the heart after intravenous injection. Subsequent modifications have attempted to estimate the volume of cardiac output by monitoring the aortic arch by means of a collimated counter after intravenous injection.[3] Nylin and Blömer[4] described the injection of labeled red cells in an arm vein with subsequent counting of periodic bilateral jugular samples; 1 of the curves produced in this manner showed sharp, symmetric peaks. This suggested that a rapidly injected substance retained some semblance of a symmetrically divided bolus even after passing through lungs and brain. Greitz,[1] as a part of a very thorough and well controlled angiographic study of cerebral circulation, described the use of intracarotid radioisotope with monitoring of the parietal parasagittal area to estimate cerebral circulation time. These results were correlated with careful analysis of serial angiograms. Such a radioisotope technic has considerable value as a research tool but has the disadvantage clinically that it requires arteriopuncture and does not study both sides simultaneously. If carotid arteriopuncture is to be done, considerably more data can be obtained by angiography.

No attempt at quantitating cerebral blood flow has as yet been made during work with this technic. It is quite possible that considerable quantitative data could be derived using the same principles as Huff and associates[3] did in estimating cardiac output.

It is planned to obtain a better shielded and more ideally collimated detection system. Considerably more development and standardization is needed. An improved apparatus for fixing the detection units precisely in relation to the head would greatly improve the test's reliability.

SUMMARY

1. A technic is described which compares the arrival in the cerebral hemispheres of an intravenously injected radioisotope.

2. The amount of radioiodine-labeled Diodrast in each hemicranium is continuously plotted by 2 collimated detectors for one minute after intravenous injection of this radioisotope. Immediate curves, largely representing right and left cerebral blood flow, are produced by a 2-channel recording galvanometer.

3. Several curves on normals and on patients with known cerebrovascular abnormalities are presented.

4. These preliminary studies suggest it may be of value as a test supplementing angiography in any condition creating a considerable dissimilarity in blood flow in 1 hemisphere relative to the other.

5. With further refinement, useful quantitative data might be obtained, making it of value in any clinical or laboratory situation in which cerebral blood flow might be of interest.

The authors wish to acknowledge the interest and assistance of Dr. Benedict Cassen and Dr. W. H. Blahd of the Radioisotope Service.

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Genetics of convulsive disorders

I. Introduction, Problems, Methods, and Base Lines

Julius D. Metrakos, Ph.D., and Katherine Metrakos, M.D.

In 1951, a study designed to assess the hereditary factors, if any, in the various epilepsies was initiated in the Department of Genetics of McGill University in collaboration with the Department of Medical Genetics of the Montreal Children's Hospital. During the first year of the investigation, in our naiveté, we thought that we were obtaining quite a number of answers. However, as our studies continued and were extended, we came to appreciate more and more the difficulties inherent in the pursuit of genetic factors in a condition as heterogeneous as epilepsy. It is, therefore, with great humility and certainly without any dogmatism that, in this and in subsequent papers, we present numerous findings, some impressions, and occasional conclusions.

INTRODUCTION

Throughout the long, tortuous, and sometimes awesome history of epilepsy, various investigators have suggested that the prevalence of convulsive disorders among the relatives of epileptics may be several times higher than that among the relatives of nonepileptics. The earlier estimates were based mainly on the presence or absence of a positive family history, often without regard to the genetic relationship of the affected individuals to the proband. This often led to reports of 80% or more of positive family histories and inevitably to the conclusion that hereditary factors were involved. The fact that a wide distribution of the epileptic symptom-complex throughout the population would have the same effect was not considered. It was not until comparatively recent years that more refined statistical approaches have been employed, in which prevalence of convulsions is measured for specific groups of relatives, such as in co-twins, other siblings, parents, and offspring of the probands.

Although most of the more recent investigators who have attempted to elucidate the hereditary factors in epilepsy agree that the prevalence of convulsive disorders and electroencephalographic abnormalities among the near relatives of some classes of epileptics may be several times higher than among the relatives of nonepileptics, few, if any, agree about the relative importance of heredity as an etiologic factor in epilepsy. There is little wonder, therefore, that no mode of genetic transmission has been postulated that is completely acceptable even to the investigator postulating it.

DIFFICULTIES AND MISCONCEPTIONS

There are 2 main groups of difficulties and/or misconceptions that account for our failure in the past to reach some agreement regarding the relative role of heredity and environment in the production of epilepsy. These difficulties stem chiefly from differences between workers in their concepts of heredity and epilepsy. It is not at all surprising that, whenever an investigator asks the question: Is epilepsy hereditary?, he obtains a slightly different answer, for each time the question is slightly different, even though its words may be the same. It would serve a useful purpose, therefore, if, in this initial paper on the genetics of convulsive disorders, the question itself: Is epilepsy hereditary? were examined from the geneticist's point of view. (At this time, only the most basic principles will be considered. More sophisticated interpretations will be dealt with later.)

Heredity vs. environment. Until fairly recently, a favorite topic of debate has been the question of whether environment or heredity was responsible for some particular human

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trait. Such a discussion implied that the concepts of environment and heredity were mutually exclusive and, if a trait was governed by one, the other could have but very little effect upon it. Thus, on the one side, the hereditarians—we have purposely not said "geneticists"—held that the germ plasm was all important, while, on the other side, the environmentalists insisted that the heredity of the organism counted for very little, especially when the organism was Homo sapiens.

However, as the science of genetics expanded and more fields were encompassed, particularly the fields of developmental and medical genetics, it became increasingly apparent that human traits, for the most part, are the result of an interplay between environmental and genetic factors. Thus, the modern genetic epileptologist investigates the epilepsies not so much from the point of view of establishing their heredity but rather from the point of view of assessing the relative roles of heredity and environment as etiologic factors in their production. Whenever the clinical epileptologist does likewise, many of the controversial aspects of heredity and epilepsy immediately become less controversial.

The interrelationship of heredity and environment has been expressed by Stern[1] as follows: "No phenotypic trait is independent of either hereditary or environmental agents, and an attempt to divide into two fractions the interrelation of two agents, neither of which alone can produce a phenotype, is logically impossible." (From a physician's point of view, the word clinical may be substituted for phenotypic.) At the risk of appearing philosophical, we may add that every genetically controlled character is dependent on at least 2 environmental factors, space and time, for its phenotypic manifestation.

Although it is true that some human characters, for example, blood groups, are clearly genetic and that their phenotype is not influenced in any appreciable way by their normal environment (environmental extremes will, of course, affect any character), most of the characters in man are not of this class. Both physical traits, such as stature and weight, and physiologic traits, such as blood pressure or susceptibility to disease, are the result of an interplay between heredity and environment and have, therefore, a wide range of phenotypic variability.

From what has been said thus far, it should be clear that, when we ask: Is epilepsy hereditary?, we are really asking: To what extent are hereditary factors important in epilepsy? And if the answer is that hereditary factors are of some importance, a statement of the degree of importance is meaningless unless restricted to a specified environment, for, to repeat the words of Stern, " . . . an attempt to divide into two fractions the interrelation of two agents, neither of which alone can produce a phenotype, is logically impossible."

If we seem to have spent too much time on this fundamental question of heredity vs. environment, it is because we consider its full appreciation of the utmost importance, particularly when attempting to elucidate hereditary factors in epilepsy.

Affected vs. unaffected. When hereditary factors are studied by following their transmission from generation to generation or by examining their distribution among closely related individuals, it is essential that the exact number of the affected and unaffected individuals within each sibship is known. Any conclusions regarding the mode of inheritance ultimately rests upon this division. Consequently, in any genetic investigation of epilepsy, it is imperative for the genetic epileptologist to identify, describe, and classify the trait to be studied as completely as possible, so that there is a clear-cut dichotomy between the terms affected and unaffected.

With apologies to all the eminent epileptologists who have investigated the diverse aspects of epilepsy, we shall forego at this time the usual review of the literature pertaining to identification, description, and classification but shall, instead, confine the discussion to some of the difficulties that are usually encountered in medical genetics when attempting to ascertain the number of affected and unaffected individuals within a particular sibship. Those engaged in the study of genetic factors in epilepsy must be prepared to meet all of these difficulties.

In the light of present neurophysiologic knowledge, it is generally accepted that all clinical forms of epileptic attacks, irrespective of etiology, have the same physiologic mech-

anisms. Essentially, we may look upon an epileptic seizure as a manifestation of excessive neuronal discharges originating within the brain and affecting a part or all of the body. Many physiopathologic sets of circumstances may be effective in triggering these discharges. As with fever, anorexia, or pain, therefore, a convulsive episode is not a disease entity but rather a symptom of disease, and, just as in fever, anorexia, or pain, the etiologic factors are varied and many. And once again the question is asked: Is heredity one of these factors? And, if so, in which of the epilepsies is it a primary factor?

It may be helpful here to consider the genes that may contribute to an individual's resistance or susceptibility to convulsions in 3 major categories.

Threshold genes. The central nervous system of man is such that any individual can be made to convulse if he is subjected to sufficient convulsant stimulation — electroshock, metrazol, hyperventilation, electrolyte imbalance, hyperthermia, infection, and so on. Since individuals differ considerably in the amount of stimulation required to effect a convulsion, it is conceivable that the convulsion threshold may be under genetic determination. Certainly, in some strains of mice, the threshold for audiogenic seizures is much lower than in other strains.[2] Such differences have also been found in other animals[3] and have even been implied for man.[4]

Cerebral disease genes. There are many known genes for specific cerebral diseases, for example, tuberose sclerosis, myoclonus epilepsy, and infantile amaurotic idiocy, in which convulsions may be one of the associated signs and symptoms. Since individual cases of any one of these genetic cerebral diseases do not necessarily exhibit convulsions as part of the syndrome, once again the role of the threshold genes must be considered.

"Epilepsy" genes. The questions that still remain and in which we are most interested are: Are there special genes specific for epilepsy? If there are such genes, in what way do they differ from the threshold genes responsible for the individual's innate capacity to convulse?

When we remember that no gene acts by itself alone but is dependent upon the whole genotype of the individual, it becomes unnecessary to mention that the genes responsible for the 3 major genetic categories of epilepsy are closely interrelated. Stated in a different way, each gene has the biochemical products of the rest of the genotype as part of its environment and is influenced by them just as by any other environmental factor.

Irregular expression of genes. It has been stated above that the keystone of any successful genetic study is the correct identification of affected and unaffected individuals. In addition to the fact that different groups of genes may be operating in the production of the various epilepsies, the phenomena of expressivity, penetrance, and chronicity combine to make the identification of affected and unaffected particularly difficult.

Expressivity. Clinically, expressivity refers to the severity of the condition. If a gene responsible for convulsions has variable expressivity, that is, produces different degrees of severity in different individuals, it is important to state clearly what minimum signs and symptoms will be accepted as identifying an affected individual. The effects of any gene that we may associate with a specific form of epilepsy may well vary from seemingly unrelated behavior patterns and other phenomena (what Pond,[5] Snyder,[6] Strotzka,[7] and others have referred to as borderlands of epilepsy or epileptic equivalents) through minor imperceptible lapses, petit mal, grand mal, and status epilepticus to death. Furthermore, this variability in clinical expression may be due partly to the expressivity of the gene and partly to the action of separate and distinct modifying genes.

The question of expressivity is further complicated by the fact that the genes responsible for a specific type of epilepsy, in addition to setting off excessive neuronal discharges within the central nervous system, may affect the individual in other ways. Such genes are said to have pleiotropic effects. Frequently, such multiple effects may appear together in the same individual or separately in different individuals.

Before leaving the question of expressivity, it is necessary to consider the number of convulsive episodes that are required before an individual is identified as affected. Is one

convulsive episode sufficient? If no bona fide clinical convulsions have occurred, what borderlands of epilepsy are sufficient by themselves to class an individual as affected? Migraine headaches? Temper tantrums? Breath-holding? Bed-wetting? Unexplained abdominal pain? Daydreaming? If we accept all of these, and especially the last, we are all "affected"!

Penetrance. Lack of penetrance refers to the phenomenon in which an individual has a genetic constitution appropriate for exhibiting a particular trait but for some unknown reason fails to express the trait in question. The expressivity of the gene in such individuals is zero, and it is extremely difficult to ascertain whether modifying genes or environmental factors are responsible for lack of penetrance. Lack of penetrance undoubtedly accounts for many so-called "sporadic" cases of known genetic conditions and is one reason why a negative family history does not necessarily mean that the condition under investigation is not hereditary.

Individuals who are genetically equipped with epilepsy genes but fail to manifest clinical epilepsy are certainly not affected from the neurologist's point of view, but they may be considered as "affected" from the geneticist's point of view, for, since they are carriers of the pathologic gene, they are "affected" with the capacity to transmit the factors in question. Geneticists do not, of course, refer to such individuals as "affected" but rather as carriers.

There is one other aspect of penetrance which, although difficult to explain adequately in a few words, must be mentioned in this general discussion of difficulties. If the frequency of the major gene for a particular type of epilepsy in a population is high but its penetrance low, the prevalence of this particular type of epilepsy will tend to be nearly the same in the near relatives of epileptics as in the near relatives of nonepileptics. In such situations, special technics are necessary to demonstrate that genetic factors are indeed in operation. On this problem, Morton[8] concludes parenthetically that "common genes with low penetrance will continue to defy precise analysis."

Chronicity. We have chosen the word chronicity to refer to the variability in the age of onset of epilepsy and also to the fact that convulsive episodes may appear, disappear, and reappear often with many years between cycles. In this sense, therefore, chronicity is a special aspect of expressivity.

Although most of the first convulsive episodes occur within the first four years of life, there is no age group that is completely immune. The geneticist is required to record the phenotypic expression whenever and wherever it occurs; although no one would think of referring to a 30-year-old man as an epileptic simply because he had several major convulsive episodes at the age of 2 but none since, nevertheless, it would be distorting the facts to say that such a person has a negative medical history for convulsions. In this respect, one must differentiate clearly between [a] prevalence—number of affected individuals at any given time; [b] incidence—number of new cases per unit of time; and [c] individual positive medical history. In epilepsy, for a given population, there are 3 separate values for these 3 parameters.

Chronicity is important in still another way, for the data of many investigators suggest that the factor of inheritance is much stronger in cases in which the first convulsions occurred during the second year of life than when they occurred later in life. This would account for the fact that in surveys such as Alstrom's,[9] in which the index cases are adult epileptics who may have had a late onset, the genetic factor is never as prominent as when the index cases are young children, as, for example, in Ounsted's[10] study. In such instances, variability in chronicity probably results in different proportions of the various forms of epilepsy in different samples and may even help in delineating the different forms.

Ascertainment, analysis, and validity of conclusions. In addion to the 2 main groups of difficulties emanating from complicatedness of gene-environment interaction, there are also the difficulties associated with the collection and analysis of the data.

Very briefly, *ascertainment* refers to how the data have been collected. In deciding how the index cases will be collected, or, in the parlance of the geneticist, how the probands will be ascertained, it is important to keep in mind the specific questions that the experiment pro-

posed to answer. For example, if we wish to know what proportion of all the epilepsies in the first two years of life are due to hereditary rather than environmental factors, we must ascertain our cases serially within this age group and by the single criterion that epilepsy is present. The cause, be it primarily environmental (birth trauma) or primarily genetic (infantile amaurotic idiocy), must have no bearing on whether the epileptic patient is ascertained. If, on the other hand, we wish to know what the risk is for a sibling of a child with a specific type of epilepsy himself becoming similarly affected, the probands must be ascertained on the single criterion that they are affected with the specific form of epilepsy under study. The importance, therefore, of stating clearly the questions that the data are intended to answer cannot be overemphasized.

It is beyond the scope of this paper to enter into a discussion of methods of ascertainment and analysis. Suffice it to say that insufficient attention here has played havoc with many a genetic investigation of epilepsy. Ideally, the ordinary methods of ascertainment and analysis have been designed for the investigation of genetic traits that are inherited in a simple mendelian fashion. In so far as most of the epilepsies probably have a complicated etiology involving a number of interacting factors, one should not expect to encounter an ideal situation to which an ordinary method of ascertainment and analysis is applicable.

Because of this vast complexity of problems and of others that might be inherent in a condition as heterogeneous as epilepsy, conclusions regarding hereditary factors must be drawn with extreme caution and in a gradual stepwise manner. In the broadest perspective, the human geneticist aims at the attainment of 3 successive steps: [a] empirical risk, [b] mode of inheritance, and, ultimately, [c] mode of gene action.

A properly controlled experiment would provide an empirical risk figure for a near relative of an epileptic having epilepsy. Comparison with the empirical risk for the same class of relative of a nonepileptic would indicate if, and by how much, the 2 risk figures differ. Finding an elevated empirical risk for a near relative of an epileptic having epilepsy would simply attest to the familial nature of the condition but would not necessarily imply genetic transmission. Certain other conditions would need to be satisfied before genetic factors are invoked and a specific genetic pattern of transmission is accepted.

If genetic factors can be demonstrated in a particular form of epilepsy and the mode of inheritance becomes known, the medical geneticist turns directly to the challenge of finding the pathways that bridge the gap between the genotype of the individual and the phenotypic expression of his clinical epilepsy.

From the practical standpoint of genetic counselling in the epilepsies, whereas a sound knowledge of the empirical risk figures is essential, a knowledge of the exact mode of inheritance and action of the gene is entirely secondary. However, it must be stressed that, if genes are responsible factors in epilepsy, an understanding of their mode of action is also essential, for herein ultimately will rest the distinction between trial and error therapy and true scientific therapy.

And now, if the reader feels fortified by the knowledge of this vast diversity of difficulties inherent in a study of the epilepsies and has not been discouraged but is still with us, we would like to direct our attention to certain general methods that have been employed in our studies of the genetics of convulsive disorders.

GENERAL METHODS

Throughout these studies, the basic question being asked has been: Is the risk for a near relative of an individual with a history of one or more convulsive episodes, with or without an abnormal electroencephalogram, significantly higher than for the same order of relative of an individual without a history of convulsions and with a normal electroencephalogram?

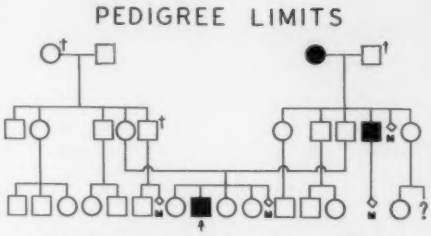
Unless otherwise stated, the epileptic probands are ascertained by examining the medical records of all patients who come to the Neurology Service of the Montreal Children's Hospital with a history of seizures. These patients are classified according to 2 major criteria based upon the clinical and electroencephalographic diagnoses. (Details of these 2 classifications will be presented in a subsequent paper.)

Selecting an appropriate control group to compare with a particular epileptic group is a difficult task but is of paramount importance in interpreting the data collected. The epileptic and control probands must be as comparable as possible in order to eliminate or randomize variable factors other than those to be studied. For example, the 2 groups must be similar for age and sex of proband, parental age, size of proband's and parents' sibship, ethnic origin, birth order of proband and parents, socioeconomic status, and many other variables, unless, of course, one or more of these factors is correlated with the presence or absence of the specific form of epilepsy under analysis.

To achieve such similarity, therefore, the control probands are drawn at random from the same hospital population to which the epileptics belong. The usual procedure is to examine the medical record of every tenth patient, and, if there is no history of convulsions, the child becomes a potential control proband. An electroencephalogram is ordered, and, [a] if the pattern is found to be within normal limits, the patient is placed in the primary control group; however, [b] if the pattern is not within the normal limits for the age of the child, the proband is accepted in one of the secondary control groups. In this way, a variety of epileptic groups (depending upon the clinical and electroencephalographic classification) is obtained for comparison with a variety of control groups (depending upon the absence of convulsions but the presence or absence of cerebral dysrhythmia).

When a suitable proband is found, epileptic or control, a family and medical history is taken by interviewing the parents and, in some cases, one or more grandparents or other relatives. In the family history, information is obtained about the parents, siblings, aunts, uncles, grandparents, and cousins of the probands (see chart). Other near relatives, such as children of siblings of the proband, offspring of cousins, and so on, may also enter the pedigree, but, unless otherwise stated, they are not considered in the analyses. Since our index cases come from a pediatric hospital, it is unlikely that there are any children of the probands.

It should be pointed out immediately that,



Pedigree illustrating all of the unaffected (unshaded) and affected (shaded) near relatives of an epileptic male proband (arrow). Dead individuals (†), miscarriages (M), and undelivered pregnancies (?) are also shown.

when one obtains pedigree data by interview with a limited number of informants, the reliability of the information leaves much to be desired. In order to improve upon the accuracy of this initial information, the following steps are taken: [1] whenever possible, a detailed investigation, including a neurologic and electroencephalographic examination, is done on the parents and siblings in both the epileptic and the control groups; [2] whenever a history of a convulsive disorder in anyone within the limits of the pedigree is obtained, an effort is made to substantiate all such reports by seeing the individual in question and/or by writing to the hospital or physician concerned; and [3] a field worker from the Department of Social Service contacts certain segments of the kindred from whom additional information is required.

At this point, 2 things must be emphasized. First, the same procedures are used and the same amount of effort expended in investigating the families of epileptic and control probands. (If any errors have been committed or any shortcomings exist, we feel that the magnitude of these is the same for both the epileptic and control groups.) Second, under the present circumstances, whereas the data and findings concerning the probands themselves, their parents, and their siblings are quite reliable, those for other relatives are far less reliable.

In a pedigree such as that illustrated in the chart, if one classifies the various relatives by sex and genetic relationship to the patient, there are 2 types of parents, 2 of siblings, 2

TABLE 1
ORDER OF GENETIC PROXIMITY TO THE PROBAND (COEFFICIENT OF RELATIONSHIP) OF 20 CLASSES OF NEAR RELATIVES

No.	Class	Coefficient of relationship for autosomal genes	Relationship to proband
1	M	.500	Mother
1	F	.500	Father
3	S	.500	Sister
4	B	.500	Brother
5	MA	.250	Maternal aunt
6	PA	.250	Paternal aunt
7	MU	.250	Maternal uncle
8	PU	.250	Paternal uncle
9	MGM	.250	Maternal grandmother
10	PGM	.250	Paternal grandmother
11	MGF	.250	Maternal grandfather
12	PGF	.250	Paternal grandfather
13	FMC/A	.125	Female maternal cousin from aunt
14	FPC/A	.125	Female paternal cousin from aunt
15	FMC/U	.125	Female maternal cousin from uncle
16	FPC/U	.125	Female paternal cousin from uncle
17	MMC/A	.125	Male maternal cousin from aunt
18	MPC/A	.125	Male paternal cousin from aunt
19	MMC/U	.125	Male maternal cousin from uncle
20	MPC/U	.125	Male paternal cousin from uncle

of aunts, 2 of uncles, 4 of grandparents, and 8 of cousins. The abbreviations that have been used by us to designate these 20 classes of relatives of the proband are listed in Table 1 in the order of their genetic proximity to the proband, expressed as the coefficient of relationship, which refers to the probability that, at a given autosomal gene locus, each of the 2 individuals has received an identical gene from the same source.[11]

If the individuals comprising a kindred such as that shown in the chart are grouped into sibships, there are the following 7 different types of sibship: I. proband's; II. mother's; III. father's; IV. maternal cousin's from aunt (MC/A); V. paternal cousin's from aunt (PC/A); VI. maternal cousin's from uncle (MC/U); and VII. paternal cousin's from uncle (PC/U). This type of consideration by sibships enables us to compare such things as sibship size, birth rank of proband, miscarriage rate, and so on, between the various sibships of control and epileptic kindred. Furthermore, it has been found that, when the age, birth rank, and sibship size of the epileptic proband correspond with those of the control proband, it usually turns out that the other branches of the 2 kindred are also comparable.

BASE LINES

It is usually stated that the prevalence of epilepsy in the general population is of the order of 1 in 200, or 0.5%. This figure appears to be the one most often quoted for various parts of the world[12] and appears to stem from Lennox's[13] earlier work based on a highly selected group, the World War I draftees of the United States Army who were rejected on the basis of having epilepsy; this figure thus relates only to those with frank, chronic epilepsy, who admitted to having epilepsy at the time of the call-up. In all probability, the figure does not include those who may have had epilepsy at an earlier age, that is, it does not include all those with a positive personal history for epilepsy.

It is well known among pediatricians that the prevalence of convulsions among children of all age groups is well above 0.5%. For example, Thom[14] found that 7% of an unselected group of children had convulsions and that such a history increases the chances of epilepsy by 5 times. Others have reported similar findings ranging from 4 to 15%. Admittedly, these figures refer, in the majority of cases, to a few episodes of febrile or infantile convulsions and not to continuing episodes as occur in chronic epilepsy. It is customary, too, when dealing with certain cerebral diseases in which frequent and often uncontrollable convulsions form only part of the syndrome, to refer to the mental retardation or motor disability without reference to epilepsy. Thus, we frequently speak of a severely retarded phenylketonuric or a greatly handicapped hemiplegic and tend to omit the epithet "epileptic," even though this may be one of the most pressing of the medical problems in the case in question. In connection with febrile convulsions, most investigators insist that such terms as "seizures" and "epilepsy" must not be employed. Quite frequently, these reluctances are based solely on an emotional desire to avoid any unpleasant connotations associated with the words "seizures" and "epilepsy."

It is evident, therefore, that here we are dealing chiefly with nomenclatorial difficulties, and, if a prevalence figure is to be given for

epilepsy, it is imperative that a precise definition of epilepsy also be given. There is no question that, clinically and prognostically, what is presently implied by febrile convulsions and what is presently implied by chronic epilepsy are very different. Nevertheless, neurophysiologically, the 2 have much in common. In so far as the 2 may also be bound genetically, the geneticist is obliged to treat the symptom-trait as one and the same until otherwise proven.

In order to obtain a base line, however rough, for comparison with the prevalence of convulsions among the patients of the hospital from which both of our experimental and control index cases are drawn and among their near relatives, the following study was carried out:

The sample. Since, in some ways, it is desirable that the size of the sample be predetermined, and also in order to facilitate calculations, it was decided to take exactly 1,000 consecutive admissions. These were serial admissions and represent children who were hospitalized for whatever reason. The sample taken comprised the first 1,000 admissions of 1956 and encompassed the period from January 1 to March 2. As is usually the case, the desired information was not available for all admissions, for it could not be obtained in 27 instances. The majority of these were adopted children. The rest were Eskimo or other children who had been flown great distances because of an accident or acute illness. These children usually arrive with a district nurse and are unattended by their parents. Here, too, the desired information is not readily available.

To make up the deficit of 27 cases, we drew from an earlier sample of 100 consecutive admissions. It is felt that the final sample of 1,000 patients is completely representative of the annual hospital population and that there have been no serious biases of selection. In no instance was the information sought not obtained because of parental refusal of cooperation.

Because of readmissions, the 1,000 admissions do not represent 1,000 separate children but only 941 (Table 2); however, all the analyses are based on the 1,000 admissions, since the questions are asked of the serial admissions and not of individual children. Hereinafter, therefore, whenever we speak of the total number of patients or total number of admissions, we are referring to same total number of 1,000 serial admissions. (Incidentally, the same analyses based on the 941 individual children did not reveal any significant differences.) Since "readmission" is here defined as a patient's name appearing more than once on the list of 1,000 admissions and not on whether he had been previously admitted, from these data one cannot estimate directly the rate of readmissions as defined by whether the patient had ever been admitted to this hospital before. All that can be said is that the rate of readmission is at least 5.9% and probably 2 or 3 times this figure.

TABLE 2

THE TOTAL NUMBER OF CHILDREN THAT ARE REPRESENTED BY 1,000 CONSECUTIVE ADMISSIONS

Number of times admitted	*Number of children*	*Number of admissions*
Once	894	894
Twice	41	82
3 times	3	9
4 times	2	8
7 times	1	7
Total	941	1,000

Of the 1,000 admissions, 637 were boys ($63.70 \pm 1.52\%$) and 363 girls ($36.30 \pm 1.52\%$). This was a most surprising finding, at least to us, for, although we expected to find more boys than girls, we did not anticipate an almost 2:1 ratio. In order to be certain that the 1,000 admissions constituted a representative sample and that we were not dealing with a seasonal variation, the percentage of males ($60.73 \pm 0.47\%$) of 11,037 consecutive admissions (June

TABLE 3

SEX RATIO OF THE PATIENTS OF THE MONTREAL CHILDREN'S HOSPITAL COMPARED WITH THAT OF THE BIRTHS OF THE ROYAL VICTORIA HOSPITAL

Hospital	*Female*	*Male*	*% Male and standard error*
CHILDREN'S			
Admissions (1956)	363	637	$63.70 \pm 1.52\%$
Children (1956)	348	593	$63.02 \pm 1.57\%$
Admissions (1954-55)	4,334	6,703	$60.73 \pm 0.47\%$
MATERNITY			
Births (1953-55)	5,246	5,464	$51.02 \pm 0.48\%$

TABLE 4

NUMBER AND TYPE OF PREGNANCIES IN THE SIBSHIPS OF PROBANDS, MOTHERS, FATHERS, AND COUSINS OF 68 "AFFECTED" FAMILIES

Sibships	Single births				Multiple births	Total	
	Live, full term	Live, premature	Still-born	Abortion		Pregnancies	Liveborn
I. Probands	158	12	1	24	1	196	172
II. Mothers	420	1	1	49	10	481	434
III. Fathers	396	2	–	32	9	439	408
IV. MC/A	279	1	1	10	2	293	283
V. PC/A	268	–	2	14	2	286	269
VI. MC/U	234	–	1	2	4	241	237
VII. PC/U	233	–	3	7	–	243	233
VIII. Parents	816	3	1	81	19	920	842
IX. MC	513	1	2	12	6	534	520
X. PC	501	–	5	21	2	599	502
XI. Cousins	1,014	1	7	33	8	1,063	1,022
XII. TOTAL	1,988	16	9	138	28	2,179	2,036

1954 to May 1956) was compared with that obtained for the 1,000 admissions. The 2 percentages are not significantly different ($P = 0.10$). The above data are summarized in Table 3.

It is not our purpose here to account for the high preponderance of boys that are admitted to this hospital. It is clear, however, that the sex ratio at this children's hospital is significantly higher than the sex ratio at birth. To illustrate this, the sex ratio in 10,710 consecutive births (April 1953 to May 1955) at the Royal Victoria Hospital was measured. The data presented in Table 3 show that the number of males (5,464) born during this period is only slightly more than the number of females (5,246), the percentage of males being $51.02 \pm 0.48\%$.

The age of each child on the day of admission was recorded to the nearest whole month by counting sixteen days and over as a whole month and by not counting fifteen days or less. The mean age of the girls (63.56 ± 2.64 months) is 4.84 months higher than that of boys (58.72 ± 1.84 months), but the difference is not significant ($P = 0.20$).

History of convulsions in index cases. For this aspect of the study, an affected individual, be he the proband or a near relative, is defined as a person who has had at least 1 convulsion, whatever the cause. In this context, a convulsion is defined as a series of involun-

TABLE 5

NUMBER AND TYPE OF PREGNANCIES IN THE SIBSHIPS OF PROBANDS, MOTHERS, FATHERS, AND COUSINS OF 132 "NONAFFECTED" FAMILIES

Sibships	Single births				Multiple births	Total	
	Live, full term	Live-premature	Still-born	Abortion		Pregnancies	Liveborn
I. Probands	390	36	3	60	21	510	457
II. Mothers	784	6	7	55	9	861	799
III. Fathers	744	–	6	31	12	793	763
IV. MC/A	578	2	2	3	12	597	596
V. PC/A	522	1	1	12	4	540	527
VI. MC/U	419	–	1	2	7	429	426
VII. PC/U	425	1	3	3	8	440	435
VIII. Parents	1,528	6	13	86	21	1,654	1,562
IX. MC	997	2	3	5	19	1,026	1,022
X. PC	947	2	4	15	12	980	962
XI. Cousins	1,944	4	7	20	31	2,006	1,984
XII. TOTAL	3,862	46	23	166	73	4,170	4,003

tary contractions of any of the voluntary muscles produced by abnormal neuronal discharges originating within the brain. Tremors or spasms of muscle groups, which may be due to peripheral local causes and in which there is no temporary loss of consciousness, are not included under this definition of convulsions. Note, too, that temper tantrums, breath-holding, and other states classified as borderlands of epilepsy are not included as criteria of an affected individual for this investigation. Here, therefore, we have set a lower limit of what constitutes an affected person. This limit is a positive personal history of having had at least 1 bona fide clinical convulsion, irrespective of cause.

In the 1,000 patients admitted, there were 115 who, upon questioning of the mother, were revealed to have had at least 1 convulsion in their life. Of these, only 30 had been admitted because of their convulsions. The rest were admitted for a variety of other pediatric conditions. The prevalence of convulsions, therefore, as defined above, for this hospital population is $11.50 \pm 1.01\%$. If patients who were admitted because of their convulsions are omitted, the prevalence is 85/970 or $8.76 \pm 0.91\%$. If the number of patients who had convulsions associated with the condition for which they were admitted is also omitted, the prevalence is reduced further to 62/974 or $6.55 \pm 0.80\%$.

History of convulsions in near relatives. The prevalence figure of approximately 10% that was obtained above represents the empirical risk that any 1 patient of this pediatric hospital would have had at least 1 convulsion for one or more of a heterogeneous array of causes. The first step in determining whether there is a familial tendency for convulsions was to test whether the near relatives of index cases with a history of convulsions are more apt to have a similar history than the near relatives of index cases without a history of convulsions.

Of the 115 patients with a history of convulsions, 68 were selected at random. We stress the randomness here with complete confidence, for it is felt that the expenditure of time and effort was the only factor that prevented us from completing the entire group of 115. Of the 885 admissions without a history of convulsions, the family histories of 132 were taken. Here, of course, it would have been quite impracticable and rather pointless to have attempted a pedigree study of all the 885 families. It must be stated, however, that the selection of the representative sample in this instance was not at random, for, although 97 of these index cases were chosen completely at random, the other 35 were included because the family histories were available, having been done routinely by some member of the Department of Medical Genetics for reasons other than this particular study. For the present purposes, we were able to find no obvious differences between the 2 groups of 97 and 35 cases and have, therefore, combined the 2.

In accord with the general methods outlined, the composition of the 7 different sibships and combinations of these for the convulsant and control groups are listed in Tables 4 and 5. Inasmuch as the trait in question could have been observed only in live born individuals, comparisons are made of the prevalence of affected individuals among the live born near relatives of the convulsant and control groups (Table 6). The comparisons are made between the 20 classes of near relatives of the probands and also for 6 combinations of these.

In every instance except 4 (PGM, MGF, FMC/U, and MMC/A), the prevalence of affected individuals is numerically higher in the convulsant group than in the control group. When the 20 classes of relatives are grouped into 5 categories (parents, siblings, aunts and uncles, grandparents, and cousins), in every instance the prevalence of affected individuals in the convulsant group is numerically higher than that in the control group. Furthermore, with the exception of the grandparents, the elevated prevalences for the convulsant group are statistically highly significant ones. When all the relatives are considered together, the prevalence for the convulsant group ($3.79 \pm 0.45\%$) is 2.9 times and significantly higher ($P = < .001$) than that for the control group ($1.31 \pm 0.15\%$).

The data strongly suggest a familial tendency, for, as the genetic distance between the relative studied and the proband increases, the frequency of affected individuals decreases (from approximately 10% in the parents and siblings to approximately 1.5% in the grandparents and cousins) in the case of the convul-

TABLE 6
PREVALENCE OF NEAR RELATIVES WITH CONVULSIONS AMONG 68 AFFECTED AND 132 NONAFFECTED PROBANDS

	Relationship to proband	Convulsant group		Control group		P+
		Number	% Affected	Number	% Affected	
1	M	68	13.24 ± 4.11	132	3.79 ± 1.67	.01*
2	F	68	5.88 ± 2.85	132	0.76 ± 0.77	.04
3	S	46	6.52 ± 3.63	153	3.27 ± 1.45	.19
4	B	58	12.07 ± 4.28	172	3.49 ± 1.41	.02*
5	MA	180	9.44 ± 2.19	328	4.27 ± 1.10	.02*
6	PA	179	5.03 ± 1.64	303	0.99 ± 0.55	.01*
7	MU	186	3.76 ± 1.38	339	1.77 ± 0.71	.17
8	PU	161	4.97 ± 1.70	328	2.13 ± 0.77	.09
9	MGM	68	2.94 ± 2.05	132	0.76 ±.0 77	.23
10	PGM	68	0.00 ± 1.05	132	0.00 ± 0.55	1.00
11	MGF	68	0.00 ± 1.05	132	0.76 ± 0.77	.66
12	PGF	68	2.94 ± 2.05	132	0.76 ± 0.77	.23
13	FMC/A	133	3.01 ± 1.48	293	0.34 ± 0.32	.05
14	FPC/A	140	0.71 ± 0.71	257	0.39 ± 0.45	.46
15	FMC/U	124	0.81 ± 0.77	212	0.94 ± 0.63	.44
16	FPC/U	115	2.61 ± 1.48	233	0.00 ± 0.32	.04
17	MMC/A	150	0.67 ± 0.63	303	0.99 ± 0.55	.40
18	MPC/A	129	0.78 ± 0.77	270	0.00 ± 0.32	.32
19	MMC/U	113	2.65 ± 1.52	214	0.47 ± 0.45	.11
20	MPC/U	118	2.54 ± 1.45	202	0.00 ± 0.32	.05
21	Parents	136	9.56 ± 2.53	264	2.27 ± 0.89	.002**
22	Siblings	104	9.61 ± 2.90	325	3.38 ± 1.00	.005**
23	Aunts and uncles	706	5.81 ± 0.89	1,298	2.31 ± 0.45	.001**
24	Grandparents	272	1.47 ± 0.71	528	0.57 ± 0.32	.130
25	Cousins	1,022	1.66 ± 0.45	1,984	0.40 ± 0.15	.001**
26	TOTAL	2,240	3.79 ± 0.45	4,399	1.31 ± 0.13	.001**

+Calculated on basis of Fisher's exact method[15] wherever necessary
*Significant **Highly significant

sant group but tends to fluctuate within fairly narrow limits around 1.31% for each class of relative in the control group.

DISCUSSION

It cannot be overemphasized that, when one seeks to demonstrate hereditary factors for a particular trait, the condition must be well defined so that affected and unaffected individuals can be readily recognized and separated from one another. The difficulty with epilepsy is that, even if there are hereditary factors involved, the symptom of convulsions may very well not be the end product of one gene but rather the endproduct of many genes, each of which, by itself or by interaction with other genes and/or environmental factors, may be capable of manifesting clinical seizures. We have already mentioned that with certain cerebral diseases this is probably the case.

Our current concepts of the neurophysiologic sequence of events in epilepsy originated with the brilliant observations of Hughlings Jackson.[16] The work of Penfield and Jasper[17] of the Montreal school and Gastaut[18] of the Marseilles school and the work of many other centers adds support to the theory that all clinical seizures, irrespective of primary etiology, have their immediate initiation in series of spontaneous, continuing, self-supporting, hypersynchronous, high frequency, neuronal discharges that can be mediated synaptically or nonsynaptically from the brain to the motor muscles. This neurophysiologic mechanism appears to be the same for all cases of convulsions. What may differ is the site of origin within the brain of the abnormal neuronal discharges and also the local or systemic stimuli that trigger these off.

The convulsions of children that are associated with hyperthermia but with no other accompanying factors used to be considered as benign and bearing no relationship whatsoever to epilepsy. In the last decade, this attitude

has gradually changed, and today the prognosis of febrile convulsions is generally held to be not as good as previously thought. Many investigators[14,19,20] have shown that an appreciable number of children with febrile convulsions may go on to have repeated attacks with fevers or even adult epilepsy. In 1953, Lennox[19] reported that more than 70% of patients with childhood febrile convulsions have some additional convulsions at a later date. From our own limited experience, we are convinced that there is no clear line of demarcation between febrile convulsions and epilepsy.

In hemiplegic patients, in whom there is presumably definite neuropathology, it is found that 50% have epilepsy along with their motor disabilities. It is of interest to note, however, that the 50% who have seizures are not necessarily the more severely handicapped physically. The distribution of mild, moderate, and severe hemiplegias is quite similar for those with epilepsy and for those without. Similarly with meningitis (or other infections) or hyperthermia, it is not necessarily the most severe cases or those with the highest fevers who will succumb to convulsions. In tuberose sclerosis, the primary etiologic factor of which is a pathologic autosomal gene, 80% of the affected individuals have convulsions, while the other 20% with lesions just as severe do not. These instances, in which a particular lesion or set of circumstances may precipitate convulsions in some individuals and not in others, clearly implicate predisposing factors influencing the convulsion threshold. The most hidden and elusive of these predisposing factors may be genes.

Because of these underlying neurophysiologic similarities that appear to be common to all types of convulsions, in this preliminary "base line" investigation, it was decided, first, to classify as affected any individual who had a history of at least one episode of clonic-tonic convulsions, and, second, not to take any pains to differentiate between the various forms of clinical seizures. Etiology was not considered nor was the electroencephalographic evidence for cerebral dysrhythmia.

The fact that the prevalence of affected individuals among the near relatives of this highly heterogeneous group of 68 convulsant probands was significantly higher than among the same order of relatives of the 132 nonconvulsant probands implies a familial distribution. We must hasten to add, however, that, because of the clinical heterogeneity and also the probable genetic heterogeneity of the material, this familial distribution is almost certainly not uniform through the material. For example, approximately 10% of the parents and siblings of the convulsant group were affected as compared with approximately 3% of the nonconvulsant group (Table 6). Now, if the familial distribution is not uniformly distributed, we should anticipate finding subgroups in which the prevalence of affected parents and siblings is higher than 10% and also some subgroups in which the prevalence is lower.

It is this type of delineation that we shall be attempting to illustrate in our next paper, in which a very specific, clinically and electroencephalographically, form of epilepsy will be considered. This is the form that the Montreal school refers to as *centrencephalic* epilepsy.

SUMMARY

1. Certain difficulties and misconceptions regarding the terms heredity and epilepsy were considered primarily from the geneticist's point of view. The 2 terms are not mutually exclusive, for a trait such as a convulsive disorder may be dependent upon both hereditary and environmental factors for its expression.

2. The difficulties of defining what constitutes an affected individual for purposes of a genetic analysis were also considered. It has been suggested that the genes responsible for convulsions may be divided into 3 major categories: threshold genes, cerebral disease genes, and "epilepsy" genes. The interaction and irregular expression of these genes may be influenced by the phenomena of expressivity, penetrance, and chronicity.

3. For the purposes of the present and subsequent papers, certain general methods of listing and comparing different orders of near relatives of convulsant and nonconvulsant probands were presented.

4. The prevalence of children with a history of having had at least 1 convulsion, among 1,000 admissions, was found to be $11.50 \pm 1.01\%$. If children who were admitted because of their convulsions are omitted, the

prevalence is reduced to $8.76 \pm 0.91\%$. The prevalence is reduced still further to $6.55 \pm 0.80\%$ if children who had convulsions as an associated symptom of their disease are also omitted.

5. The prevalence of individuals with a history of having had at least 1 convulsion among most of the different orders of near relatives of convulsant patients of a pediatric hospital was significantly higher than that for the near relatives of nonconvulsant patients who were drawn from the same hospital population. When all the near relatives (parents, siblings, aunts and uncles, grandparents, and cousins) are considered together, the prevalence for the convulsant group ($3.79 \pm 0.45\%$) is 2.9 times and significantly higher ($P = < .001$) than for the control group ($1.31 \pm 0.15\%$).

6. It is concluded that the data strongly suggest a familial distribution for convulsions among the near relatives of this highly heterogeneous group of children with a history of convulsions; however, the distribution is probably not uniformly distributed throughout all the families.

If one begins at the beginning, we take great pleasure in expressing our sincere thanks to Dr. Preston Robb, Director of the Department of Neurology of the Montreal Children's Hospital, for not only suggesting the feasibility of this investigation to us but also for his continued support and encouragement throughout its many phases.

The nature of these investigations, which we have grouped under the general title of Genetics of Convulsive Disorders, is such that, without the assistance and cooperation of many people, it could never have been conducted. In this initial paper, therefore, we wish to express our sincere thanks to all those who, in one way or another, greatly facilitated our work. Without any reference to specific individuals and yet with many such in mind, we extend our deepest gratitude to the staff of the Montreal Children's Hospital, who in no less than a thousand and one ways have contributed directly to our study. Our thanks also go to the administrators of the Maternity Division of the Royal Victoria Hospital for permitting us to examine their birth records of new arrivals. And, finally, we wish to thank the directors of the Rockefeller Foundation, the Dominion-Provincial Public Health Fund of Canada, and the National Institutes of Health of the United States of America for their financial assistance and for their patience in awaiting results.

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Chemical concomitants of convulsive activity in the cerebrum

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LABILE cerebral constituents have been studied in several laboratories by the technic of liquid air fixation. These investigations have revealed certain chemical changes that appear to be associated with generalized convulsive activity of whatever origin. Cerebral lactic acid increases in all cortical seizures so far studied. Phosphocreatine invariably shows a tendency to break down to inorganic phosphate and creatine, although the extent of this change may be small. These changes have been observed in several mammalian species and in seizures induced by a variety of convulsant drugs as well as by electroshock.[1-5] In some species, cerebral glucose and glycogen decrease significantly, these changes being presumably related to the increased rate of oxidative metabolism during the seizure as well as to glycolysis. The adenosine triphosphate level also may decrease, with formation of a small amount of the diphosphate. It is unlikely that any of these changes plays a causative role in the initiation of the seizure. The data, though limited, suggest that these reactions do not precede the electrographic changes but rather represent a parallel manifestation of the convulsive activity. A small increase in the cerebral ammonia level likewise occurs in association with most types of seizures.[6,7]

The cerebral store of acetylcholine decreases in most seizures, probably as a result of an increased rate of release and hydrolysis of this transmitter substance.[5,8,9] A notable exception, however, occurs in the seizures induced by the anticholinesterases. Here acetylcholine accumulates and appears to be the stimulating agent responsible for the increased irritability leading to the seizure.[5] This finding puts anticholinesterase seizures in a special class, distinguishable from others by its chemical pattern, although the electrographic changes are very similar to those of other types.

A second chemically distinct type of seizure is that induced by "fluoro" compounds such as the fluoroacetates. Studies of these seizures have revealed a great increase in the cerebral level of citric acid.[10] No such change has been observed in seizures induced by convulsants of other types. The increase in citrate is due to inhibition of the enzyme aconitase by the fluorocitrate metabolically elaborated and the resulting interference with the Krebs oxidative cycle.[11,12] The accumulated citrate, however, does not appear to be the actual convulsing agent.[13] Fluoroacetate seizures also are characterized by a much greater increase in cerebral ammonia than are other types.[14] This change, which occurs before the seizure begins, must be considered a possible cause of the convulsive activity.

Thus, it is possible to distinguish different types of seizures on the basis of specific chemical patterns, even though the electrographic manifestations are all very much alike. Further examples will be noted in later paragraphs.

It is desirable to extend the pertinent observations to include more cerebral constituents as well as more convulsing agents. The material to be presented consists of new data obtained in studies of seizures induced

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This work was supported by Grant B-818 from the National Institute of Neurological Diseases and Blindness, U. S. Public Health Service, and by the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation.

Read before the Sections of Neurochemistry and Neuropharmacology at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

by picrotoxin, pentylenetetrazol (Metrazol), methyl fluoroacetate, and methyl fluorobutyrate.

METHODS

The experiments were done on male dogs. Morphine was given in a dose of 5 to 6 mg. per kilogram subcutaneously and transient thiopental anesthesia was induced for the preliminary surgical procedures. The cranium was opened and the bone removed over a wide area to expose the cerebral hemispheres, the dura remaining intact. The electrocorticogram was obtained by monopolar recording, usually from 3 cortical areas. The electrocardiogram also was recorded. Blood pressure readings were taken from a cannulated femoral artery.

After the thiopental effect had disappeared, the animal was still under morphine but was susceptible to seizures. At this time the convulsant was injected intravenously. Dosages used were pentylenetetrazol, 50 mg. per kilogram and picrotoxin, methyl fluoroacetate, and methyl fluorobutyrate, 1 mg. per kilogram. An endotracheal tube permitted the use of a respiration pump when necessary during a seizure. At the chosen time, the brain was frozen with liquid air. The adequacy of the arterial oxygenation was judged from the color of a blood sample withdrawn at this time. The exposed cortical areas of the frozen brain were removed to a depth of about 1 cm. and ground together while in the frozen state to provide a uniform sample for all of the analyses. Further details of these procedures have been given elsewhere.[4]

The results are to be compared with those of control experiments that were comparable in all respects except that no convulsant was administered.

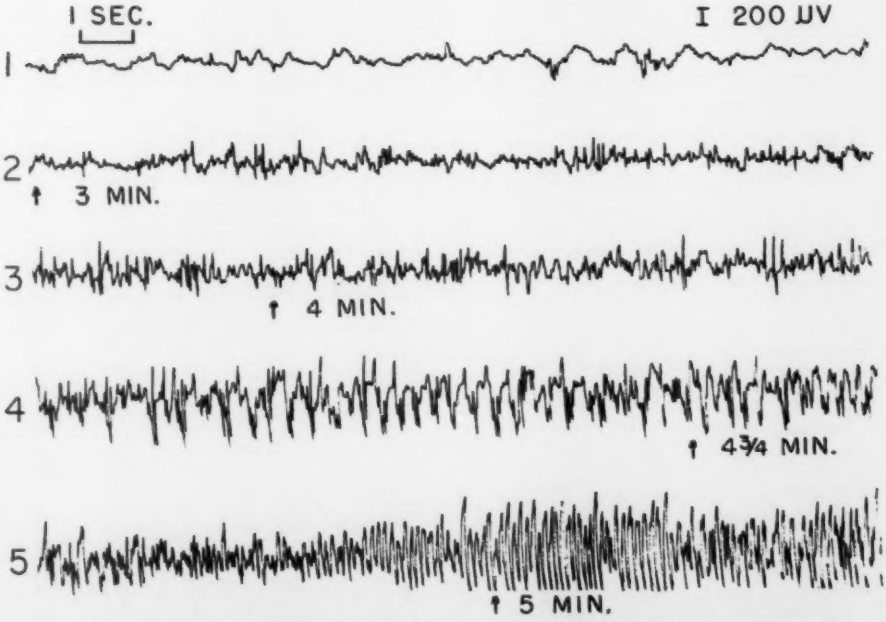
The chromatographic method of Busch, Hurlbert, and Potter[15] was used in a modified form for the study of acid metabolites. This procedure employs a Dowex 1 anion exchange resin. The column length was increased, and the mixer system for the formic acid eluent was arranged so that the concentration increased at a gradually increasing rate. Aspartic and glutamic acids, which are eluted together from Dowex 1, were separated by rechromatographing with Dowex 50 according to the procedure of Moore and Stein.[16] Acetylaspartic acid, after elution from the Dowex 1 column, was hydrolyzed with hydrochloric acid and determined as aspartic acid by chromatography on Dowex 50.[17] The ninhydrin method of Yemm and Cocking[18] was employed for all determinations of amino nitrogen. Only malic acid could be determined directly by titration after elution from Dowex 1. Citric, ascorbic, and dehydroascorbic acids were not quantitatively recovered, and other nonvolatile acid metabolites were not present in quantities large enough to be so measured or were not adequately resolved. Citric acid was determined by a procedure essentially the same as that of Buffa and Peters.[10] Ascorbic and dehydroascorbic acids were measured by the method of Schwartz and Williams.[19] The methods used for lactic acid, acid-soluble phosphates, acetylcholine, ammonia, and glutamine have been noted previously.[4,5,20] The "nucleotide phosphorylation ratio" is the molar ratio of acid-labile phosphate to ribose in the calcium-insoluble fraction; for the ribose determination, the orcinol method has been newly standardized with pure preparations of adenosine triphosphate and adenylic acid. While the procedures used do not distinguish individual nucleotides, adenosine triphosphate is known to constitute the major portion. A ratio of 2 would indicate full phosphorylation, that is triphosphates, while a ratio of 1 would represent diphosphates only. Monophosphates are found only in very small quantities and are not in the calcium-insoluble fraction.

PICROTOXIN

After injection of picrotoxin, there is a slow "build-up" in the cortical electrical activity, characterized by increasing amplitude and appearance of spikes and large slow waves. Under the conditions of these experiments, the initial changes appeared between ninety seconds and five minutes after injection. The spikes and slow waves increased gradually in size and frequency thereafter (see illustration). Muscular twitching was not noticeable in association with the initial electrographic changes, even when these were recorded from an electrode in the motor region, but twitching appeared early during the "build-up" period. It increased

thereafter in company with the developing electrographic pattern, merging into severe epileptiform activity of the clonic type. In some experiments, the clonic seizure continued for as long as twelve minutes before being interrupted by freezing. In other instances, the clonic seizure was of shorter duration and the onset of a severe tonic-clonic or grand mal seizure supervened, as in the figure. The arterial blood pressure usually showed a mild increase during the "build-up" period and a further increase in tonic-clonic seizures.

Chemical studies were preceded by 4 experiments in which depth electrodes were used to record the action of picrotoxin on various parts of the brain. In 1 instance, the dog was paralyzed with Flaxedil, 2.5 mg. per kilogram intravenously, to eliminate movement artifacts and was maintained by artificial respiration. In this limited exploration, recordings were obtained from the thalamus, head of the caudate nucleus, hippocampus, reticular formation of the rostral tegmentum, fornix, and posterior part of the corpus callosum, as well as from various cortical areas. In each instance, the brain was fixed by perfusion with formalin in situ before the electrodes were removed. We are grateful to Dr. Konrad Akert for identifying the locations of the electrode placements. The records showed the gradually increasing excitation occurring nearly simultaneously in all of these regions, suggesting that picrotoxin produces a generalized increase in excitability of the brain. An individual spike, slow wave, or burst of spikes frequently appeared in several leads at the same instant. However, the recording procedures were not capable of indicating the origin of the activity. In some of these experiments, the convulsive activity was interrupted at intervals by periods



Electrographic effects of picrotoxin, recorded from an electrode on the anterior portion of the left hemisphere. Times represent minutes after injection. 1. Control record, just before injection. 2. Early stage of excitation; muscular twitching not yet apparent. 3. Part of "build-up" period; muscular twitching associated with spikes. 4. Clonic convulsion. (This often lasts much longer.) 5. Beginning of tonic-clonic convulsion.

TABLE 1

EFFECTS OF PICROTOXIN AND PENTYLENETETRAZOL ON CEREBRAL CONSTITUENTS

Constituent	Picrotoxin: Build-up to clonic seizures			Picrotoxin: Tonic-clonic seizures			Pentylenetetrazol: Tonic-clonic seizures		
	No. of experiments	Mean	±Standard deviation	No. of experiments	Mean	±Standard deviation	No. of experiments	Mean	±Standard deviation
Lactic acid	11	1.52*	.39	6	3.20*	.31			
Phosphocreatine	10	2.45	.40	6	1.99**	.27			
Acid-labile nucleotide phosphate	10	5.92	.44	6	5.61	.29			
Nucleotide phosphorylation ratio	2	1.83		2	1.80				
Inorganic orthophosphate	10	2.86	.54	6	3.07	.28			
Acetylcholine	10	5.28*	1.17	6	5.59**	.90			
Ammonia	8	.31	.10	3	.33	.08	3	(.70)*	.18
Glutamine	8	5.77	.75	3	5.46	.13	3	(3.78)	.52
Glutamic acid	3	8.53	.68	2	7.67		6	6.74*	.51
Aspartic acid	3	2.10§	.14	2	2.00§		6	2.11	.42
Acetylaspartic acid	3	6.50	.10	2	5.85		6	5.84	.98
Malic acid	3	.78	.08	2	.78		6	.58**	.14
Citric acid	3	.22	.03	2	.22		7	.24	.06
Ascorbic acid	3	.82	.06	2	.80		5	.80	.12
Dehydroascorbic acid	3	.09	.01	2	.09		5	.12	.08

Mean values for acetylcholine are given in micromoles per kilogram of brain; for all other constituents, in micromoles per gram of brain. "Nucleotide phosphorylation ratio" is the molar ratio of acid-labile nucleotide phosphate to ribose in the calcium-insoluble fraction.

*Statistically significant differences from control values in Table 2 ($P < .01$)
**Statistically significant differences from control values in Table 2 ($P < .05$)
§Mean of all 5 picrotoxin experiments differs significantly from control value ($P < .01$)
Values in parentheses are from a previous publication.[11]

TABLE 2

EFFECTS OF METHYL FLUOROACETATE AND OF METHYL FLUOROBUTYRATE ON CEREBRAL CONSTITUENTS

Constituent	Fluoroacetate seizures			Fluorobutyrate seizures			Control experiments		
	No. of experiments	Mean	±Standard deviation	No. of experiments	Mean	±Standard deviation	No. of experiments	Mean	±Standard deviation
Lactic acid	10	(5.39)*	2.28	8	5.55*	1.02	15	1.04	.28
Phosphocreatine	10	(1.47)*	.40	2	1.25		13	2.28	.28
Acid-labile nucleotide phosphate	10	(5.10)*	.50	2	5.12		13	5.85	.34
Nucleotide phosphorylation ratio				2	1.66		3	1.77	.06
Inorganic orthophosphate	10	(3.98)*	1.08	2	4.16		13	2.88	.43
Acetylcholine	10	4.69*	1.66	2	4.17		13	6.68	1.03
Ammonia	6	(1.34)*	.47	7	1.65*	.45	10	.26	.08
Glutamine	6	(3.98)	.80	7	5.19	1.84	10	5.51	1.96
Glutamic acid	5	7.56	1.12	7	7.12	.88	10	7.94	.77
Aspartic acid	5	1.63*	.40	7	1.53*	.18	10	2.38	.20
Acetylaspartic acid	5	6.99**	.79	7	6.01	.69	11	6.18	.61
Malic acid	4	.65	.24	5	.86	.06	9	.78	.17
Citric acid	10	(1.25)*	.31	7	1.26*	.10	8	.24	.02
Ascorbic acid	5	.73**	.10	8	.84	.06	12	.86	.09
Dehydroascorbic acid	5	.07	.03	8	.10	.03	12	.09	.02

Mean values for acetylcholine are given in micromoles per kilogram of brain; for all other constituents, in micromoles per gram of brain. "Nucleotide phosphorylation ratio" is the molar ratio of acid-labile nucleotide phosphate to ribose in the calcium-insoluble fraction.

*Statistically significant differences from control values ($P < .01$)
**Statistically significant differences from control values ($P < .05$)
Values in parentheses are from previous publications.[6, 11]

of nearly isoelectric or slow wave patterns. These intervals were nearly simultaneous in all leads.

Chemical findings in picrotoxin-injected animals are summarized in Table 1. Data on control animals are given in Table 2, which includes all of the pertinent control data obtained in this laboratory to date. During the "build-up" period, cerebral lactic acid increased and acetylcholine decreased significantly. Aspartic acid also appeared to be slightly decreased. The other observed constitutents remained in normal ranges. In this series, freezing was done at times ranging from the appearance of incipient changes, ninety seconds after injection of picrotoxin, through the development of severe clonic seizures, the longest period being twenty-five minutes. The increase in lactic acid developed progressively during the "build-up," but the decrease in acetylcholine did not seem to be correlated with time or intensity of electrographic changes. Aspartic acid values were obtained at only six, eight, and nine minutes. No changes were found that seemed to be causative or to reveal causative processes in the convulsive response.

During tonic-clonic seizures, the lactic acid was further increased. Acetylcholine remained low but did not show a further drop. The phosphocreatine was reduced significantly, but the increase of inorganic phosphate was not statistically significant in this group. Acid-labile nucleotide phosphorus and phosphorylation ratio were not reduced. When the aspartic acid levels of the "build-up" and tonic-clonic groups are taken together, the mean is significantly lower than that of the controls. The slight increase in ammonia was not statistically significant, but Richter and Dawson[6] found a significant increase during picrotoxin seizures in brains of rats.

PENTYLENETETRAZOL

Since pentylenetetrazol induces a severe tonic-clonic seizure within ten to twenty seconds after intravenous injection, this drug appears to differ from picrotoxin with regard to the latent period of its action. However, as shown by Preston,[21] the electrographic pattern of the picrotoxin seizure, including the "build-up" to a clonic seizure, can be mimicked by a slow intravenous infusion of pentylenetetrazol.

Chemical findings in the tonic-clonic pentylenetetrazol seizures are very similar to those in picrotoxin convulsions. Previous studies on dogs under slightly different conditions have demonstrated lactic acid formation, phosphocreatine hydrolysis, no changes in the nucleotides or phosphorylation ratio, and a decrease in acetylcholine.[2,5] Of the constituents measured in the present series (Table 1), acetylaspartic, citric, ascorbic, and dehydroascorbic acids and glutamine showed no significant changes. The mean for aspartic acid was slightly low, as in picrotoxin seizures, but in the pentylenetetrazol group this change was not statistically significant. Glutamic and malic acids were reduced by small but significant amounts during pentylenetetrazol seizures, while such changes did not appear with picrotoxin. Ammonia was increased more by pentylenetetrazol than by picrotoxin.

METHYL FLUOROACETATE

Methyl fluoroacetate induces an extremely violent tonic-clonic convulsion. The onset is preceded by a latent period, the duration of which was fifty-three to eighty-eight minutes under the conditions of these experiments. Electrographic records of the convulsive cortical activity have been published by Chenoweth and St. John.[22] During the latent period, the citrate and ammonia levels were found to be increasing in the brain.[4,14] Lactic acid and phosphocreatine remained unchanged until the seizure began, although the acid-labile nucleotide level was slightly low.[4] Similar findings in rats have been reported by Dawson and Peters.[23]

The changes found during seizures are shown in Table 2. Citric acid and ammonia were very high. Lactic acid was increased, splitting of phosphocreatine was evident, the acid-labile nucleotide was slightly decreased, and the acetylcholine level was lowered. Aspartic acid was decreased, suggesting that this substance is a possible source of ammonia, but the change was not great enough to account for all of the ammonia formed. Acetylaspartic acid showed a significant increase and ascorbic acid a slight decrease.

Dawson[24] has observed a similar decrease in

aspartic acid in brains of fluoroacetate-poisoned rats. He also found a significant decrease in glutamic acid, and the sum of glutamine and alanine was increased.

METHYL FLUOROBUTYRATE

The toxic effects of methyl fluorobutyrate closely resemble those of fluoroacetate. The only obvious difference is that the latent period preceding the seizures is shorter with fluorobutyrate, being twenty-five to thirty-eight minutes under the conditions described. Electrographic patterns from brain and heart are the same for the 2 convulsants.

Chemical changes occurring in the brain during fluorobutyrate seizures likewise were found to be very similar to those induced by fluoroacetate. There were the same high levels of citrate, lactate, and ammonia and the same decrease in aspartic acid. The phosphate analyses were done in only 2 experiments, these being sufficient to demonstrate the breakdown of phosphocreatine and the slight decrease in acid-labile nucleotides. The nucleotide phosphorylation ratio also was determined and was found to be slightly decreased in each of these 2 experiments. Acetylcholine was determined in 2 instances and was found to be reduced.

Fluorobutyrate did not induce significant changes in ascorbic and acetylaspartic acids. Thus, in respect to these 2 constituents, the effects of fluoroacetate were not duplicated by fluorobutyrate. The meaning of these differences cannot be assessed at this time. However, the major similarities leave little doubt that fluorobutyrate blocks the Krebs cycle as does fluoroacetate. The shorter latent period could be due to a more rapid entry into the brain or, more probably, to a more rapid entry into the metabolic cycle, since the initial steps for butyrate are different than those for acetate.

BLOCKING OF SEIZURES BY ATROPINE

Atropine in large doses has been shown to have a blocking action on seizures induced by various cholinesterase inhibitors. Specifically, in the dog under the conditions of these experiments, the convulsive action of tetraethyl pyrophosphate was blocked by atropine sulfate in a dose of 6 mg. per kilogram intravenously.[5] Pentylenetetrazol seizures, however, were not blocked by atropine.

In further experiments with atropine, dogs were prepared as described previously except that the brain was not exposed. The electrographic changes were recorded from electrodes consisting of screws inserted into small drill holes in the exposed calvarium. Atropine sulfate in doses of 6 mg. per kilogram intravenously was found to be ineffective against the seizures induced by injections of picrotoxin, methyl fluoroacetate, and methyl fluorobutyrate. In each instance, a second dose of atropine of the same magnitude, given while the convulsive activity was in progress, failed to block the seizures.

DISCUSSION

On the basis of the available data, the following tentative classification is suggested for seizures that are induced by pharmacologic agents.

Anticholinesterase seizures. These are characterized by the accumulation of acetylcholine in the brain. The unique nature of this type is confirmed by the specific action of atropine, which blocks these seizures but fails to block any of the others so far studied.

Seizures induced by fluoro-fatty acids. These are characterized by inhibition of the enzyme aconitase and the resulting accumulation of citrate in the brain and by a large increase in the cerebral ammonia. Both fluoroacetate and fluorobutyrate induce these changes and thus appear to act by the same basic mechanism despite minor differences. If it could be proved that accumulating ammonia is the causative factor, these seizures would be classed with those induced by the injection of ammonium chloride.[14]

Picrotoxin-type seizures. Picrotoxin and pentylenetetrazol have not been shown to have specific effects on intermediary metabolism that might account for their convulsive action. They do not affect oxygen uptake or glycolytic mechanisms of surviving brain slices or suspensions, except at concentrations far greater than could exist in the extracellular fluid after a convulsant dose.[25,26] McLennan and Elliott[27] observed stimulating effects of these agents on the synthesis of free acetylcholine in brain slices and cell-free extracts at concentrations

that might be attained by convulsant doses. This was demonstrated in the presence of eserine. The level of "bound" acetylcholine was not altered in their experiments. These findings are difficult to reconcile with the decreased level of total acetylcholine that occurs in vivo during seizures. It is of interest that the decrease precedes the convulsive activity, being present during the "build-up" period after injection of picrotoxin. This change apparently is related to the heightened state of excitability. However, the failure of atropine to block the seizures indicates that the convulsive activity is not to be explained in terms of cholinergic mechanisms.

It seems reasonable to tentatively class picrotoxin and pentylenetetrazol seizures together as representing a type for which unique and characteristic chemical changes have not yet been revealed. The slight differences in chemical pattern between the drugs can be regarded as of minor importance until further studies substantiate them and reveal their meaning. No chemical change has so far been revealed that distinguishes these seizures from those induced by electroshock, a "nonchemical" stimulus, although it must be noted that some of the chemical constituents discussed here have not been measured after electroshock. Conceivably, picrotoxin and pentylenetetrazol mimic the action of an unknown chemical transmitter at certain central synapses.

Seizures of pyridoxine deficiency. Convulsions occur in pyridoxine deficiency in human infants[28] as well as in experimental animals. Similar convulsions are induced by thiosemicarbazide and other hydrazides. Administration of pyridoxine counteracts the effects of convulsive hydrazides as well as those of dietary deficiency. Killam[29] has summarized various studies of these effects. Pyridoxine is essential as a precursor of pyridoxal phosphate, which acts as a coenzyme in the reaction by which glutamic acid is decarboxylated to form gamma-aminobutyric acid. When the coenzyme concentration is reduced or when its action is blocked by a hydrazide, the level of gamma-aminobutyric acid in the brain is reduced. The low concentration of this inhibitory substance appears to be the critical factor that precipitates the seizure. The fact that no decrease in gamma-aminobutyric acid occurs in pentylenetetrazol seizures[29] or in fluoroacetate poisoning[24] suggests that the convulsions related to reduced pyridoxal phosphate activity represent a distinct type. It should be noted that Preston[21] has been able to distinguish between the electrographic effects of thiosemicarbazide and those of pentylenetetrazol; when the former is applied to the cortex and the latter is then injected, the effects are not additive or competitive but seem to be independent of each other.

Strychnine-type seizures. The effects of strychnine appear to be different from those of most other known convulsants. Work of Eccles and his associates[30] suggests that strychnine may exert its effects by blocking the action of an unknown "inhibitory transmitter." The transmitter in question probably is not gamma-aminobutyric acid. Sufficient data are not available to delineate a chemical pattern associated with strychnine convulsions. Tetanus toxin, brucein, and thebaine may act in the same manner as does strychnine.

Methionine sulfoximine seizures. It appears likely that the convulsive activity induced by methionine sulfoximine is related to the special metabolism of methionine,[31] but further studies are necessary to reveal the chemical pattern and elucidate the convulsive mechanism.

Other possible types. There are many known convulsants that cannot be classified until more data are available. It is probable that these include types not yet distinguished.

SUMMARY

Certain chemical changes in the brain appear to be characteristic of intense convulsive activity, being found in seizures induced by a variety of convulsants. Other changes are specific for the type of convulsing agent used; hence, it is possible to classify seizures in accordance with chemical patterns, each type showing its own characteristic chemical changes, although the electrographic patterns of the various types may be indistinguishable. A tentative classification on this basis is outlined for seizures induced by pharmacologic agents. Pertinent data on seizures induced by picrotoxin, pentylenetetrazol, methyl fluoroacetate, and methyl fluorobutyrate are presented. These data have been obtained by analysis of dog cerebral tissue frozen in situ.

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Neurologic aspects of the Möbius syndrome

A case study with electromyography of the extraocular and facial muscles

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THE UNUSUAL SYNDROME of congenital facial diplegia with restriction of horizontal eye movements has been the subject of speculation and interest which has continued to be active since the first description by A. von Graefe in 1880.[1] Although this syndrome has been described under such headings as congenital facial diplegia, oculofacial paralysis, congenital paralysis of the sixth and seventh nerves, and nuclear agenesis, it does not lend itself to a brief accurately descriptive term. The designation of Möbius[2,3] as the eponym is justified, since he first suggested that congenital bilateral abducens-facial paralysis might be an independent pathologic entity. This he did after comparing his original case with that of von Graefe and that of Chisholm.[4] Later he described other cases of cranial nerve palsies under the presumptive term of *infantilen Kernschwund*. He did not clearly distinguish between congenital and acquired conditions, and his concept of pathogenesis, that is nuclear degeneration, has not been supported by the meager pathologic studies thus far available.

Most recent authors would agree with the following description: The Möbius syndrome involves a variable degree of facial paralysis with inability to abduct the eyes beyond the midpoint. Partial atrophy of the tongue and other deformities about the face and head are often present. Paralysis of the soft palate and muscles of mastication may occur. Absence of pectoral muscles, talipes, syndactyly, and other extremital deformities are common. Mental deficiency occasionally accompanies the physical defects, but signs related to long-fiber tract involvement are seldom seen. The condition is congenital and nonprogressive. Henderson[5] and Danis[6] have tabulated the various deformities and the relative frequence of their occurrence and association.

A description is not complete, however, without elaboration of the peculiar nature of both the facial paralysis and the restriction of eye movements. The paralysis of the face is nearly always bilateral, often asymmetric, and tending when incomplete to spare the lower face and platysma. Many authors have commented not only on this peculiar distribution of paralysis but on the usual lack of sagging of the face and the absence of contractures which are seen in acquired facial paralysis. When electrical stimulation has been employed the response of the areas of preserved activity has been roughly proportional to the degree of voluntary movement possible. Reaction of degeneration has not been reported. The facial paralysis seen in cases of congenital facial diplegia without other defects is characterized by the same features.[5,7]

Inability to abduct either eye beyond the midpoint is the other cardinal feature of the syndrome. This is particularly striking since conjugate movements in the vertical plane are often normal or nearly so. Convergence is, as a rule, present to varying degrees, even though adduction may be absent or much weaker in lateral gaze. Pupillary responses are normal. Bell's phenomenon is commonly present. Nystagmus is seldom seen, and horizontal nystagmus has not been elicited by vestibular stimu-

Presented in part at a meeting of the Midwestern Section of the Association for Research in Ophthalmology, St. Louis, April 20, 1958.

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lation when this has been tested. Ptosis has been noted in only a few cases. Vision and the fundi are generally normal, and diplopia is not a symptom.

It has been common to refer loosely to these defects in ocular motility as abducens paralysis or external rectus paralysis. However, in almost every case where the deficits in ocular movement have been described in detail, it has been evident that they are based on a more complicated pathologic mechanism than simple paralysis of the external rectus muscles. Often evidence of paralysis of lateral gaze is found. Henderson, in his extensive review,[5] did not refer to this possibility, but it was noted that convergent squint was not present in about half of the instances of abducens paralysis. External ophthalmoplegia was noted in 15 of the 61 tabulated cases of facial diplegia.

Many contributors to this subject[6,8–21] and authors of textbooks in ophthalmology, such as Duke-Elder[22] and Walsh,[23] accept a neurologic defect as basic to this syndrome. Some have commented in particular on the supranuclear nature of the ocular pareses.[6,8,10,13,14,21,23] However, the question as to whether the defects are primarily mesodermal or ectodermal arose after the first case reports. Lennon[24] suggested that, since the associated defects appeared to be of mesodermal origin, probably the oculofacial defects were similarly based, i.e., primarily muscular rather than nuclear.

A serious challenge to the assumption that the syndrome is characterized by developmental defects primarily in the central nervous system is implicit in the occurrence of congenital absence or defective insertion of extraocular muscles or in fibrosis of these muscles. Ford[25] expressed the opinion that fibrosis of muscular tissue in the nonsagging face characteristic of congenital facial diplegia may be responsible for the facial paralysis and be comparable to the fibrosis of extraocular muscles in Duane's syndrome. He favored the view that the syndrome is based on primary muscular changes.

Richards[26] failed to find muscle tissue in biopsies in the region of the frontalis in 3 cases. He pointed to the consistently incomplete involvement of the oculomotor nerve with preservation of function of the medial rectus muscle and concluded for these and other reasons that the basic defect was a peripheral dysplasia of muscle.

Evans[27] reported 9 cases of cranial nerve pareses of congenital origin, some of which are representative of this syndrome. Concentrating on an embryologic analysis, he stated that congenital deficiency of muscles derived from the first 2 branchial arches seemed more likely to be responsible for the deformities than did primary nuclear aplasia. Lennon, Richards, and Evans did not discuss their cases from the standpoint of detailed analysis of eye movements or possible gaze paralysis.

The paucity and incompleteness of pathologic studies relating to this syndrome are responsible for the continued speculation and disagreement in regard to pathogenesis. Necropsy studies being insufficient, supplementary methods of examination are of special significance and deserve consideration as a source of information. Electromyography has been employed in only 2 previous cases,[9,11] and the eye muscles have been studied by this method in only 1 other instance.[9] The following case is reported as a contribution to the knowledge of the Möbius syndrome because justifiable inferences relating to the nature of the primary defect may be drawn from the data provided by a series of examinations, including electromyography of the extraocular muscles.

CASE REPORT

A 26-year-old white male was first observed at the State University of Iowa Hospital in 1931 at age 5 weeks. He was the sixth child of parents in their 20's. The other children were well. Delivery had been spontaneous after a short labor. Birth weight was 9 lb. The infant was admitted for correction of clubbed feet, but there had been difficulty in nursing and poor nutrition.

Examination disclosed malnutrition and bilateral talipes equinovarus. Convergent strabismus was noted. One side of the tongue was larger than the other. The upper lip was prominent and the mouth was open much of the time. Xerosis of the corneas and chronic conjunctivitis were noted. The corneal reflexes could not be elicited and there was infrequent blinking. Routine laboratory studies and the blood Kahn test were negative.

He continued to take feedings poorly and gained weight slowly. At age 6 months he was regarded as mentally defective. Operative correction of the clubbed feet was undertaken. Inguinal hernias were noted. At age 4 the I.Q. was 50, toilet training was delayed, and he could say only a few words. The patient was placed in a state school for retarded children and was not seen again until 1957, when he was admitted for inguinal herniorraphy.

The patient was a well-developed, muscular young man. The gait was normal but he was less agile than the average male of 26. His responses were simple and childlike. He was quiet, unobtrusive, and dependent. The speech was dysarthric and difficult to understand. Convergent strabismus with hypertropia on the left associated with immobility of the facies was quite striking. The skin of the face was oily and perspired freely. The lids could be only partially closed voluntarily but there was no ptosis. Excepting slight upward movement of the left eye on command, no movement of the eyes was seen on command, on attempting to follow an object, or on efforts to elicit reflex movements. There was no Bell's phenomenon. Bilateral purulent conjunctivitis was evident, with exposure keratitis on the right. A dense cataract on the left, the result of an old injury, rendered this eye blind. The right pupil reacted to light; the left did not. The size of the pupils was equal. Vision on the right was 6/60 and the fundus was normal.

The face was completely immobile except for twitching in the right upper lip. The face did not sag (Fig. 1). Sensibility of the face to touch, pain, and temperature and that of the corneas to pain was intact. The masseters were poorly developed but jaw closure was strong. However, the mouth was usually open. The palate was high and the soft palate moved actively. The tongue was protruded poorly and was atrophic, markedly so on the right, with longitudinal furrowing and fasiculations. There were no other neurologic abnormalities. The second, third, and fourth digits of the right hand were short, with fusion of the distal phalanges. Correction of clubfoot had been successful, with surgical scars evident. The general physical examination was otherwise not revealing except for a small left inguinal hernia.

Fig. 1. The patient, a 26-year-old male. There is no sagging of the face. Asymmetrical atrophy of tongue and convergent squint are evident. Virtually no movement of eyes could be elicited. (By permission of Charles C Thomas)

Routine laboratory studies showed normal values. Roentgenograms of the skull and cervical spine revealed no abnormalities. The vocal cords moved well. The hearing seemed normal, but audiography was unsatisfactory because of poor cooperation. Although vertigo apparently resulted from douching the ear canals with hot and cold water, no nystagmus was induced.

The electroencephalogram revealed a low-voltage fast record and normal sleep record. No occipital alpha wave was seen. Faradic and galvanic stimulation of facial musculature and facial nerves produced no movement whatsoever even when the arm to which the electrode was applied was caused to move by the current. Electrooculograms were attempted, but no potential changes were noted on command to movement, on efforts to follow an object

with the eyes, or on attempt to elicit optokinetic nystagmus with a rotating drum.

A lateral tarsorraphy was done on the right to protect the cornea. A biopsy of the lid and levator palpebrae showed only a fragment of muscle. The left external rectus muscle, resected to correct esotropia, appeared normal grossly and microscopically. Forced duction tests established that this eye could be moved passively. Before the operative procedures were done, electromyography of the extraocular and facial muscles was performed.

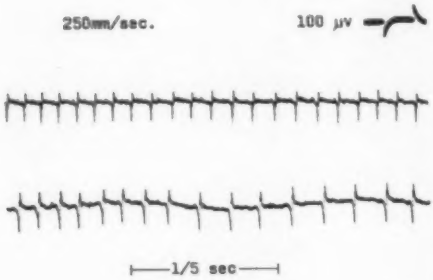

Fig. 2. External rectus muscle, right eye. This record demonstrates repetitive firing of a single unit which was initiated by probing with the needle electrode. This activity continued for over a minute and was easily reproducible. It was frequently interrupted by bursts similar to that shown in Figure 3. The 2 tracings are probably representative of the same motor unit with slightly different needle placement.

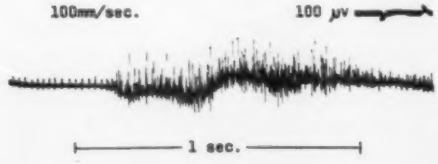

Fig. 3. External rectus muscle, left eye. Spontaneous short-lived volley of motor units. This type of activity is never seen in normally innervated extraocular muscle in the waking state. It betrays the presence of many motor units.

ELECTROMYOGRAPHIC STUDIES OF EXTRAOCULAR AND FACIAL MUSCLES

Method. The muscle action potentials were recorded with a concentric 27-gauge-needle electrode inserted directly into the extraocular muscle through the conjunctiva. The patient was in a shielded room, and the potentials were led to 2 identical 4-stage capacity coupled amplifiers. The resultant signals were displayed on the tube of a 2-channel oscilloscope so that the potentials of 2 muscles could be observed simultaneously. Photography was accomplished on continuously moving paper with use of the Grass C4D kymograph camera.

Results. The following extraocular muscles were studied: the right and left external rectus, the left internal rectus, and the right inferior rectus. Action potentials were found in all muscles tested. The activity manifest in the external rectus muscles was quite anomalous and similar on the two sides. A few low-voltage action potentials were found on first insertion of the electrode. However, probing with the needle resulted in brief bursts of action potentials, betraying the presence of a greater number of motor units. This activity, while considerable, was less in respect to the number of potentials than that of a normal extraocular muscle.

Once stimulated to activity by needle insertion, the external rectus muscle on the right quickly became quiescent, but after several probings it displayed a persistent firing of 1 to 3 motor units, continuing for perhaps a minute (Fig. 2). The external rectus muscle on the left showed a similar response when stimulated by needle movement but also soon displayed a continuing activity which spontaneously waxed and waned in intensity. This spontaneous activity was frequently punctuated by sudden bursts of potentials from motor units firing in relatively large numbers. These volleys (Fig. 3) were of a duration varying from 0.7 to 1.5 seconds and recurred at intervals of 1.7 to 8.5 seconds. After several volleys the activity might subside steadily and rapidly to electrical silence or to that of a single small unit which fired repetitively for a period to be joined suddenly and spontaneously by many units to produce another volley. These spontaneous bursts or volleys were much like those elicited by probing the muscle.

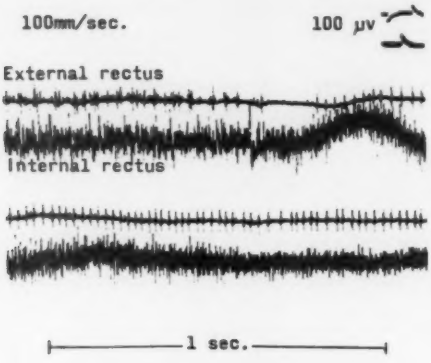

Fig. 4. External and internal rectus muscles, left eye, recorded simultaneously. Lower 2 tracings are continuous with upper 2. Level of activity of internal rectus is greater than that of external rectus. Record was made with patient at rest, without effort to induce eye movement. At other times our efforts to induce lateral movement resulted neither in visible change in position of the eyes nor in changes in electromyographic record.

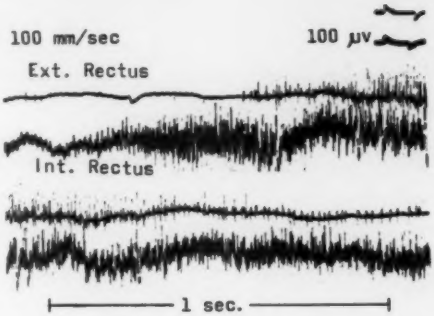

Fig. 5. External and internal rectus muscles, left eye, recorded simultaneously. Record is continuous. Note spontaneous volley in external rectus muscle, with simultaneous waxing of activity in internal rectus. There is no evidence of normal reciprocal innervation.

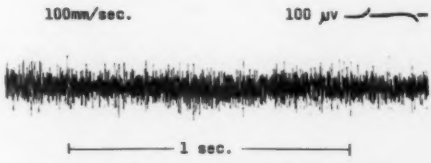

Fig. 6. Inferior rectus muscle, right eye. This motor unit activity was evident immediately on entering the muscle. Amplitude of potentials and their number suggests a normally innervated muscle. Spontaneously varying levels of activity were not evident.

The internal rectus muscle on the left manifested the constant high rate of firing of multiple potentials typical of a normal extraocular muscle. This activity was evident immediately on entering the muscle. Ebb and flow of potentials was present but not so prominent as that in the external rectus of the same eye (Fig. 4). Command to move the eyes or to follow an object caused no change in motor unit activity.

Motor unit potentials were recorded simultaneously from the external and internal rectus muscles on the left, as seen in Figures 4 and 5. The record in Figure 4 was made after the almost silent external rectus muscle was stimulated to activity by electrode movement. The internal rectus muscle required no stimulation. These records show lack of the normal patterns of reciprocal innervation and displayed no change when an attempt was made to elicit eye movement. In Figure 5 an example of spontaneous activity at rest is seen, with near simultaneous volleys appearing in both muscles. At other times a tendency for spontaneously increasing activity to occur in both muscles at approximately the same time was evident. A record of potentials taken simultaneously from the internal and external rectus muscles of one eye in a normal subject is shown in Figure 9 for comparison.

The right inferior rectus muscle displayed a constant high level of activity of a nature and degree typical of normally innervated muscle (Figs. 6, 7). Slight variation in the record was observed on command to move the eyes up and down, although the eye was not seen to move (Fig. 7). Spontaneously changing levels of activity were not seen.

Although no voluntary contraction of facial muscles was evident, and no contraction was seen on strong electrical stimulation, motor unit potentials were obtained from the right

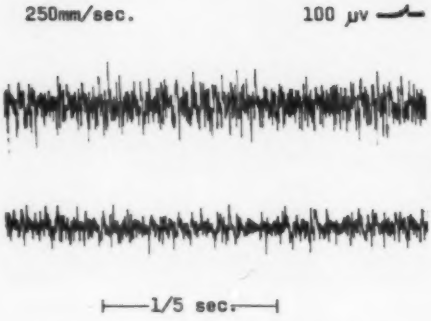

Fig. 7. Inferior rectus muscle, right eye. Record shows further activity of this muscle with different needle placement. Tracing is not continuous. Upper record demonstrates level of activity at rest and lower record shows some decrease in activity on command to upward movement. Eye was not seen to move. This shows the only evidence of reciprocal inhibition obtained by our examination. (This tracing was obtained at a faster rate of movement of recording paper than that in Figure 6.)

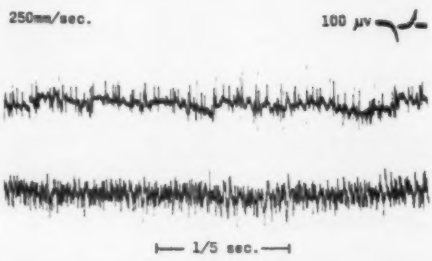

Fig. 8. Facial musculature: orbicularis oculi, right eye. Record demonstrates motor units in musculature of lid. Activity was stimulated by probing with electrode. Tracings are not continuous but demonstrate different levels of activity which occurred spontaneously and with no apparent relationship to command to close the eyes. It is of interest that strong electrical stimulation over the facial nerve, done previously, caused no visible contraction of this musculature.

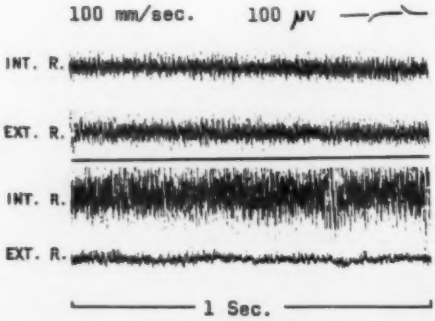

Fig. 9. External and internal rectus muscles, left eye, normal subject. Recorded simultaneously for comparison. Upper tracing shows essentially equal and constant activity of normal amplitude in both muscles. Lower tracing was taken when eye was turned strongly into field of action of internal rectus. Note increased motor unit activity of this muscle and corresponding reciprocal decrease in activity of external rectus.

orbicularis oculi (Fig. 8). As in the external rectus muscles, potentials were evident after stimulation by electrode movement. There was some spontaneous ebb and flow of activity as well. There was no change after command to close the eyes. No electrical activity was found in the regions of the left frontalis or of the right orbicularis oris muscles.

PARALYSIS OF OCULAR MOVEMENTS

The electromyographic studies show that the external rectus muscles, which might have been assumed to be fibrous, displayed many motor unit potentials.* The transient firing of motor units on irritation by the needle electrode and the spontaneous ebb and flow of activity after several manipulations of the electrode suggest a supranuclear lesion. The absence of any change in motor unit activity that could be correlated with a command to attempt movement of the eyes lends further support to this supposition. The record of potentials from the left internal and external rectus muscles taken at the same time clearly

*Breinin[9] reported the electromyographic examination of an infant 1½ years old who exhibited the Möbius syndrome. In his case the lateral rectus muscles revealed few potentials and a gritty sensation on electrode insertion which he interpreted as evidence of fibrosis of the muscle.

demonstrates nearly simultaneous bursts of activity. This record shows a striking violation of normal reciprocal innervation. The brief volleys seen in Figure 3 resemble the spindles recently described by Breinin[28] and found by him in extraocular paralysis of a supranuclear type. The records do not present conclusive evidence of a deficiency of the abducens nucleus, but the paucity of potentials compared with those of the other muscles suggested this possibility, as did the esotropic position of the eyes.

The conclusion that ophthalmoplegia in our patient was due, in large part, to a supranuclear lesion seems to be well established. It could not have been determined by inspection of the patient whether absence of eye movement was due to a supranuclear, nuclear, or infranuclear lesion, or to aplasia, fibrosis, or defective attachment of the muscles. However, the normal histologic appearance of the rectus muscle and passive mobility of the eye which failed to move on vestibular stimulation justify the inference that a supranuclear lesion was present. This reasoning was employed by Yasuna and Schlezinger[21] in discussing 2 cases of the syndrome. The findings were similar, although there were vertical movements and convergence. Little adduction was seen on lateral gaze, but the eyes could be moved passively. The external rectus muscles appeared normal at operation, and microscopic examination revealed changes consistent with a mild degree of atrophy. These authors suggested that the Möbius syndrome is the result of a brain stem lesion which is predominantly supranuclear in respect to function of the abducens nerves and nuclear or infranuclear in respect to the facial nerve.

In the first case described by von Graefe,[1] lateral associative eye movements were quite deficient and only a suggestion of abduction beyond the midline was noted. Vertical movements were relatively normal, and convergence was intact. He attributed the much more efficient action of the internal rectus muscles in convergence than in lateral associative movements to disuse of the latter movement because of longstanding paralysis of the external rectus muscles. He noted that although both abducens nerves were paralyzed the eyes were not in convergence.

The original patient of Möbius[2] was an adult who, like the patient of von Graefe, presented bilateral facial palsy. The eyes were in normal position and vertical movements were well performed. Convergence movements were strong. Lateral movements were absent, but adduction could be obtained on command to follow an object with one eye covered. This movement was found to be only a part of convergence, since the covered eye adducted as well. The condition was congenital. Möbius suggested that the anomalous eye movements in his case could be due to a nuclear lesion of the abducens nerves and a central paralysis of the oculomotor nuclei in reference to the internal rectus muscle.

Schapringer[29] in 1889 described a girl with congenital paralysis of the face and inability to rotate the eyes laterally. Vertical movements and convergence were unimpaired. He considered the term bilateral abducens paralysis "insufficient and misleading" and proposed the term bilateral pleuroplegia.

The failure of vestibular stimulation to cause nystagmus is considered to be due to an interruption of the posterior longitudinal fasciculus, and in the pathologic studies of Heubner[30] and of Riggs[31] this structure was found to be grossly deficient or absent. The concept of internuclear paralysis in reference to the ability of the internal rectus to contract well in convergence but not in lateral gaze has been firmly established with reports of associated lesions in the pontile tegmentum.[32,33] The case of Reese and Yaskin[34] is especially pertinent. Their patient suffered from an intramedullary tumor of the pons. She had a moderately convergent position of the eyes, normal vertical movements with normal convergence and accomodative reflexes, but loss of movement in lateral gaze. There was no response to vestibular stimulation. There was right facial paresis and the tongue was small and showed fibrillations. In addition, there was ataxia and evidence of long-fiber tract involvement.

The characteristic deficits of ocular movement in the Möbius syndrome can justifiably be attributed to a lesion of the brain stem. In our case, as in others previously described, ophthalmoplegia was virtually complete and disassociated function of the internal rectus muscles was not demonstrated. The electro-

myographic findings have been offered as evidence of a central paralysis. Variability in extent of supranuclear and nuclear dysplasia could account for the difference in signs from one case to another. The important point is that evidence of a supranuclear and/or internuclear lesion clearly implicates the central nervous system as the primary site of disease or malformation in this syndrome insofar as paralysis of ocular movement is concerned.

PARALYSIS OF THE FACE

The presence of motor unit activity in the orbicularis oculi of our patient deserves comment. The spontaneous motor unit discharges, varying degrees of activity, and failure of this activity to correlate with command to movement suggest that the facial paralysis is in part supranuclear. The paucity of potentials correlates with the concept of an imperfectly developed facial nucleus. Hellstrom[11] found a few motor units in an area of the face where paralysis appeared complete, and Breinin[9] reported a few insertion potentials in the orbicularis oculi of an infant presenting this syndrome. The existence of action potentials in an immobile area of the face which does not show muscular contraction even on electrical stimulation of the nerve is strange, although Bonar and Owens[35] and Meucci and Giordano[14] have reported instances where high intensities of current caused contraction in otherwise immobile areas. There seems to be no other explanation for our findings than that strands of innervated muscle enmeshed in fibrous tissue could not by their contraction produce detectable movement. In some areas muscle may be absent.

The peculiar distribution of congenital facial paralysis has been the subject of frequent comment. The relative sparing of the lower face and platysma is not a feature of the usual lower motor neuron lesions and is the converse of the characteristic preservation of movement in the upper face in supranuclear paralysis. The "nonanatomic" nature of this facial paralysis has been used as an argument that the basic defect cannot lie in the central nervous system.[26,36] In the few pathologic studies that have been made, the facial nuclei have been found to be absent in whole or in part or to be deformed.[30,37]

In searching for an anatomic substratum for this distribution of paralysis, attention must be turned to the structure of the motor nucleus of the facial nerve. Papez[38] has studied the various divisions of the facial nucleus in mammals and has found that the ventromedial and ventrolateral nuclei of this nerve degenerate when lower fibers of the peripheral nerve are sectioned. He concluded that "the facial nucleus of mammals follows a common plan of subdivision associated with the differentiation of the facial musculature and branches of the facial nerve." The studies of Vraa-Jensen[39] essentially support this proposition.

The recent report of Richter[40] concerned an infant with paralysis of the right side of the face and other anomalies. The facial nerve was not seen. The only abnormality in the brain stem was virtual absence of the right facial nucleus, with a few normal neurons in its caudal portion. There was no evidence of degeneration, and the author felt that the basic lesion was congenital hypoplasia. Is it not possible that the peculiar distribution of congenital facial paralysis may be based on a differential involvement of the subdivisions of the motor nucleus?

Atrophy of the tongue which is often asymmetrical and accompanied by fasiculation, as in our case, suggests a nuclear deficit. So, too, does atrophy of the muscles of mastication[20] and the musculature of the pharynx.

PATHOLOGIC FINDINGS IN THE MOBIUS SYNDROME

While no formal challenge has been made concerning the justification for regarding the Möbius syndrome as a unique entity, the divergent views as to pathogenesis constitute an indirect challenge and lead to confusion. One cannot establish a special defense for the singularity of the syndrome. The bizarre association of defects must speak for itself as being beyond the likelihood of coincidence.

An examination of the arguments for a primary neural defect as opposed to a primary muscular dysplasia can possibly be of value in reconciling these two views. Only a few brains have been available for examination.[5] Heubner[30] reported his studies on the brain of a 1½-year-old boy. The face was masklike, with complete paralysis on the left and partial

on the right. There was complete paralysis of both abducens nerves and atrophy of the left half of the tongue. The defects were apparent at birth and nonprogressive. There were no other neurologic deficits, although motor development had been generally retarded. The pathologic studies disclosed extensive changes in the brain stem. The medulla and pons were asymmetrical (smaller on the left). The left hypoglossal, left facial, and both abducens nuclei were markedly deficient in cells. The right facial and hypoglossal nuclei were more nearly normal. The trochlear and oculomotor nuclei were only slightly involved. The posterior longitudinal fasciculus was virtually absent. The sensory nuclei were intact. These findings confirmed the supposition that the paralyses were related to nuclear lesions. Heubner found no evidence of inflammation or degeneration and concluded that hypoplasia was responsible for the neural defects.

Spatz and Ullrich[37] examined the brain of an infant who had ptosis, masklike facies, immobility of the eyes, and webbing of the fingers. Changes of a dysplastic nature were seen in the oculomotor, trochlear, abducens, and facial nuclei.

While dysplastic changes were present in other cases related to this syndrome[40,41] and in the case of Riggs[31] the number of examinations has been so small that conclusions must be cautiously drawn. However, no autopsy report is on the record where the brain stem has been normal in the Möbius syndrome.

Pneumoencephalography has shown abnormal enlargement of the basal cisterns in two cases.[11,15] Electroencephalography has revealed abnormalities in several instances,[8,11,16,18] but in the case reported by Van Buskirk[20] it was regarded as normal.

Leszynsky[42] (1897) is often quoted as an early challenger of the concept of nuclear degeneration as the cause of congenital paralysis of ocular movement. He pointed out that nuclear atrophy can be secondary to dysplasia of muscle. Bedrossian and Lachman[43] reported on an adult who could not move his eyes in a lateral direction. Optokinetic nystagmus was absent and stimulation of the vestibules resulted in a "decreased response." The facies were "slightly" masked. Forced duction tests under general anesthesia revealed that the eyes were immovable laterally. There was thickening of Tenon's capsule and of numerous check ligaments about the medial and lateral rectus muscles which were inserted "slightly more posteriorly than normal." They cited these findings as clear evidence that the pathologic process in their case was peripheral in the muscles. This case may not be a typical example of the Möbius syndrome.[21]

The occurrence of congenital absence, faulty attachment, and fibrosis of ocular muscles[44–46] is well known, and fibrosis of the external rectus muscle is considered by many as the essential pathologic process in the Duane retraction syndrome. In several cases of the Möbius syndrome, biopsy of the extraocular muscles has been done. The findings have been variable but perhaps not inconsistent. In Hicks's[12] case there was pronounced limitation of lateral rotation. The lateral rectus muscles were thin and lacked tone but were not fibrous. In Stansbury's[19] case there was convergent strabismus. Horizontal motion was limited. There was greater adduction on convergence than on lateral gaze. The 4 rectus muscles of the left eye appeared normal in size, texture, and tone. The 2 patients of Yasuna and Schlezinger[21] were found to have normal-appearing lateral rectus muscles. In one case reported by Reed and Grant,[16] lateral eye movements were nearly absent. Elevation, depression, and adduction were free to forced duction, but abduction was limited. The lateral rectus was a fibrous band. The medial rectus was thickened and contracted.

Of interest is the possible relationship of this syndrome to arthrogryposis mutiplex congenita,[18,26] a condition that has been attributed to both nuclear dysplasia[47] and muscular dystrophy.[48] The patient reported on by Sprofkin and Hillman[18] had divergent strabismus with no horizontal eye movement and no convergence. Vertical eye movements were unimpaired. There was weakness of the face, ankylosis of the knees in flexion, and cavovalgus deformity of the feet. The lateral rectus muscle was represented by a few strands of tissue, and the medial rectus was inelastic.

One may reasonably assume that lack of innervation due to nuclear hypoplasia, and at times immobility due to supranuclear paralysis, will result in secondary changes in the extra-

ocular and facial muscles. Hence, there is no evidence that the oculofacial manifestations of the Möbius syndrome are not due to a nonprogressive congenital disorder of the nervous system that is of unknown etiology. The evidence that they are based on a lesion of the brain stem is virtually unassailable.

It must be recognized, however, that occasional cases of congenital muscular dystrophy or dysplasia may, by coincidence, present functional losses and deformities resembling those of the syndrome under discussion. It would seem reasonable and logical to keep such cases separate from those where, by one means or the other, it is possible to demonstrate central nervous system involvement.

SUMMARY

1] An example of the Möbius syndrome has been presented. Electromyographic examination of the extraocular and facial muscles provided information of distinct value in the understanding of the neuromuscular disorder.

2] The absence of ocular movement in this case is attributable in large degree to supranuclear paralysis and in lesser degree to nuclear deficiency. Electromyography provided substantial support for this impression gained from clinical and surgical findings. Many case reports, including those of von Graefe and Möbius, describe elements of gaze paralysis. It is reasonable to assume that supranuclear paralysis of ocular movement is an important though variable feature of this syndrome. Hence, we may repeat the admonition of Schapringer (1889) that the term bilateral abducens paralysis is "insufficient and misleading."

3] Evidence of extensive deficiency of muscle tissue in the face and suggestive evidence of supranuclear paralysis of the residual musculature was obtained by electromyography. The failure of this musculature to demonstrate visible contraction on electrical stimulation may be the consequence of entrapment of scattered fibers in fibrous tissue. The unique tendency for sparing of the lower face in the congenital facial diplegia of this syndrome may be related to a differential involvement of the subdivisions of the facial nucleus.

4] While in certain instances congenital malformation of muscle or muscular dystrophy may simulate the disorder under discussion, there is no evidence that the oculofacial manifestations of the Möbius syndrome are not based on a disorder of the nervous system. There is excellent reason to believe that they are so based. The best evidence is the histologic demonstration of disordered formation of supranuclear structures. This is well supported by clinical and laboratory signs of central paralysis of the eye movement.

ACKNOWLEDGMENT

We wish to express our appreciation to Drs. O. R. Hyndman and R. J. Joynt for helpful suggestions and to Messrs. Charles Deutsch and Miss Helen McInnery of the Medical Illustration Service, Veterans Administration Hospital, Iowa City, for technical assistance.

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Radiologic aspects of Dandy-Walker syndrome

Giuseppe Scarcella, M.D.

THE DANDY-WALKER syndrome is a specific type of hydrocephalus, due to prenatal obstruction of the foramina of Luschka and Magendie, in which the radiologic findings are considered to be pathognomonic.

Dandy and Blackfan[3] in 1914 demonstrated for the first time the clinical picture of this type of hydrocephalus, and, later, Dandy[4] described its surgical treatment. Taggart and Walker[14] in 1942 reported on 3 personal cases and 6 cases collected from the literature, giving an excellent embryologic explanation of this condition and emphasizing particularly its roentgenographic findings. Coleman and Troland[2] in 1948 reported on 2 patients of 14 months and 17 years of age, respectively, successfully operated upon. In these cases, the exact diagnosis was not made preoperatively and the true nature of the lesion was recognized only at the time of the operation. In Russell's monograph[11] on the pathology of hydrocephalus, 1 autopsy case of obstruction of the foramen of Magendie is mentioned and the opinion is expressed that "this condition appears to be rare."

Further papers[1,5,6,7,9,10,12,13,15,16] on the subject in recent years would indicate that this condition is more common than has been thought in the past. Benda[1] in 1954 reported that, in his observations, atresia of the foramen of Magendie represented the most common type of congenital hydrocephalus: the analysis of his last 13 autopsies of hydrocephalic children showed that 6 were cases of Dandy-Walker syndrome, 3 were cases of Arnold-Chiari malformation, and the remaining 4 were due to aqueduct stenosis (2 cases), fibromatosis (1 case), and epitheliomatosis (1 case). It would seem then that the Dandy-Walker syndrome is still little known and very seldom recognized during life. Most of these cases are probably regarded as having hopeless noncommunicating hydrocephalus and excite no further interest.[12]

The following 2 cases of atresia of the foramina of Luschka and Magendie were recognized and operated upon recently in the Blue Bird Clinic. These cases led to this report, with the particular purpose of illustrating the characteristic radiologic aspects leading to precise preoperative diagnosis.

Case 1. (B-590) A 10-month-old Negro baby was born one month postmaturity by breech presentation and application of forceps for the aftercoming head. The baby did not cry immediately, and oxygen was given for two days. Before the child was 4 months old, the mother noticed that his head was growing rapidly and that its size was larger than that of any of her 6 previous children. From the fourth month on, the size of the head increased slowly. At the time of admission, the head circumference was 57.5 cm. There were suture separation and enlarged anterior and posterior fontanels (3 x 2½ and 1 x 1½ in.).

Skull x-rays in the AP projection revealed enlargement of the vault with marked suture separation (Fig. 1A); in the lateral projection, extreme thinning of the occipital bones was noted, with more marked enlargement and bulging of the posterior cranial fossa (Fig. 1B).

Indigo-carmine test showed free interventricular communication, but no dye was obtained by lumbar puncture. Protein content in the lumbar cerebrospinal fluid was 9 mg. per cent.

Ventriculography showed absence of the septum pellucidum in the AP projection and marked symmetric ventricular dilation; the upper part of the aqueduct was also visualized and appeared dilated (Fig. 2). In the lateral projection, the aqueduct was visualized again and appeared markedly dilated; this communicated with a large cystic formation in the posterior cranial fossa, outlining the surface of a small cerebellum. The

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Read at the eighth meeting of the Italian Society of Neurosurgery, Rome, November 10, 1957.

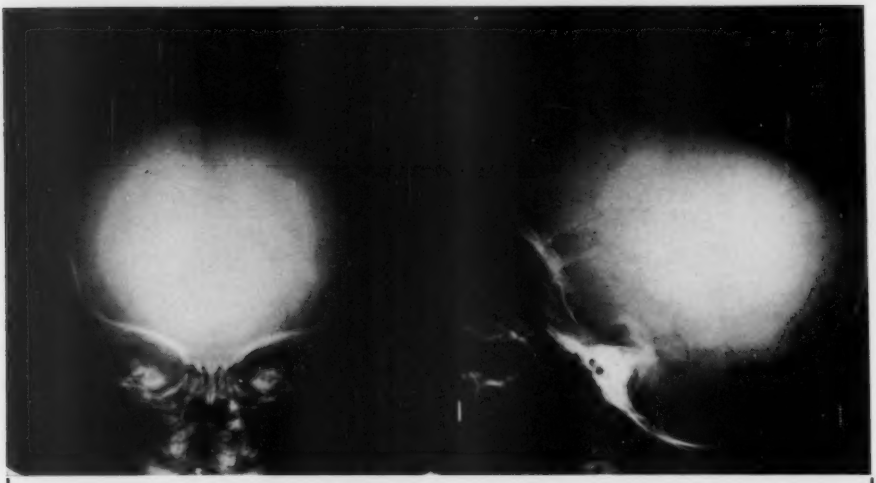

Fig. 1. *(Case 1)* Anteroposterior projection *(left)* reveals enlargement of the vault and separation of sutures. Lateral projection *(right)* shows marked enlargement and bulging of posterior fossa.

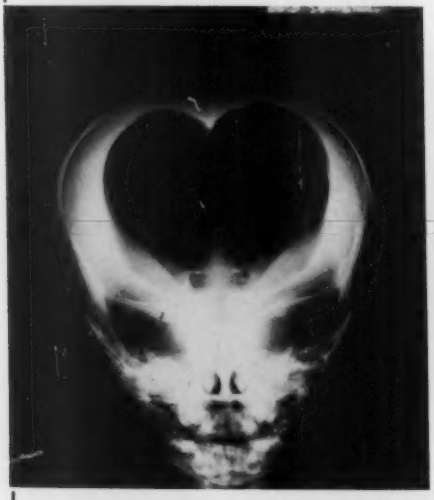

Fig. 2. *(Case 2)* Symmetric ventricular dilation. Aqueduct is also visualized and appears dilated.

Fig. 3. *(Case 1)* Lateral projection of the ventriculogram revealing dilation of the aqueduct, an extremely large cystic formation in the posterior fossa, and upward displacement of inferior horns of lateral ventricles. All these radiologic signs are considered pathognomonic of the Dandy-Walker syndrome.

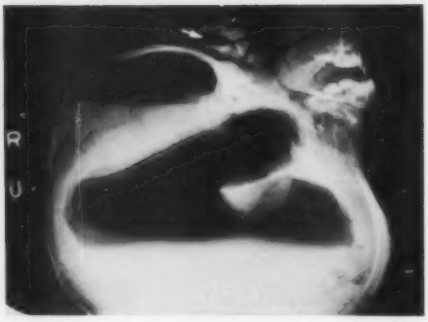

Fig. 4. *(Case 1)* Vertex-down projection showing the limits of the cystic formation in the posterior fossa and its projection into the cervical canal (arrow)

tentorium appeared to be elevated, and the posterior temporal and occipital portions of the lateral ventricles were pushed upwards (Fig. 3). Projection made with the patient inverted (upside-down position) showed the gas level in the large posterior fossa "cyst" and the projection of the "cyst" into the upper cervical canal (Fig. 4, arrow).

Operation. A large suboccipital craniectomy revealed that the transverse sinus was located in a position much higher than normal; instead of a midline occipital sinus, there was a pair of occipital sinuses, 1 on the right and 1 on the left, about 1½ in. apart at the upper end of the exposure and converging into the region of the craniocervical junction posteriorly. These were of considerable size. The dura was tight, thin, and bluish and formed the outer membrane of a tremendously large "cyst" in the posterior cranial fossa. The tentorium appeared markedly elevated, being about 2 in. above the exposure. The cerebellar hemispheres were extremely reduced in size, and, around the foramina of Luschka and Magendie, there were thin-walled membranes extending down

Fig. 5. *(Case 1)* Surgical exposure of the membranes of the cyst, which are continuous with the floor of fourth ventricle and extend superiorly toward the tentorium and downward to C2 level. Note the space between the small cerebellum and the occipital bones after escape of a large amount of cerebrospinal fluid.

Fig. 6. *(Case 2)* Lateral x-ray projection of skull showing a V-shaped fracture in the parietal bone and marked separation of lambdoid sutures

Fig. 7. *(Case 2)* Lateral projection of the ventriculogram revealing a tremendous amount of air completely filling the posterior fossa. Tentorium and transverse sinuses are elevated.

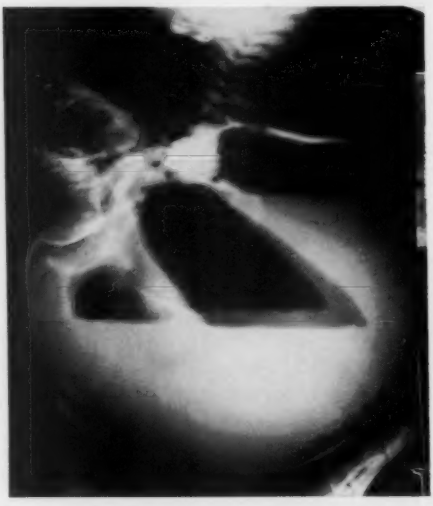

Fig. 8. *(Case 2)* Vertex-down projection showing the limits of the posterior fossa cyst, obliteration of the cisterna magna, and absence of air in the spinal subarachnoid spaces

to the level of C2 and obstructing any communication between the cranial cavity and the spinal subarachnoid space. These membranes were stripped away and detached; they appeared to be in continuity with the fourth ventricle (Fig. 5). The anterior medullary velum of the cerebellum was converted into a thin membrane and curved upon itself. It was continuous with the membrane that lined the cystic cavity. The aqueduct was easily visualized and appeared enlarged. All membranes around the base of the cerebellum were removed, and the portion separating the spinal canal from the cranial cavity was excised; it was then possible to pass a catheter down the spinal canal.

Case 2. (55.19247) A Latin-American male infant born after thirty-nine weeks' gestation was delivered following a total of sixteen hours, forty minutes' labor under cyclopropane anesthesia by a ROA mechanism with low forceps. At birth, the head was 44.5 cm. in circumference, molded with a prominent vertex. The anterior fontanel measured 6 x 6 cm. and was not bulging. The sutures were widely separated. The pupils were equal and reacted to light. The cry was strong when the child was stimulated and a sucking reflex was present. The Moro reflex was sluggish. The infant moved all 4 extremities.

At the age of 4 days, skull x-rays revealed gross enlargement of the calvarium. In the lateral projection, a large V-shaped fracture was present in the parietal bone with separation of the fracture lines. There was marked separation of the lambdoid suture, but the frontal bones appeared less prominent as compared with the more pronounced bulging in the posterior part of the skull (Fig. 6).

Three weeks later, a subdural puncture through the anterior fontanel failed to reveal any blood collection. Indigo-carmine test showed free inter-

ventricular communication while no cerebrospinal fluid was obtained by lumbar puncture. The ventricular fluid contained 178 mg. per cent protein.

Ventriculography revealed marked dilation of the lateral and third ventricles; a very large amount of air collected in the posterior fossa. The limits of the cerebellum could not be established. Tentorium, torcula, and transverse sinuses appeared extremely elevated (Fig. 7). In the head-down position, a large amount of air filled what seemed to be a cystlike formation in communication with the ventricular system. The cisterna magna appeared completely obliterated, and no air was seen in the spinal subarachnoid spaces (Fig. 8). Radiologic diagnosis was: "This probably represents a ballooned roof of the fourth ventricle due to obstruction of the Luschka and Magendie foramina as described by Dandy and Walker. Conclusion, Dandy-Walker syndrome."

Operation. Suboccipital craniectomy revealed a tremendous cystic cavity occupying most of the posterior fossa. When this cyst was opened, 2 small cerebellar hemispheres were visualized unfused in the midline, so that there was no vermis present. Membranes were firmly attached to the lower margin of the fourth ventricle, extending on the surface of the cerebellum toward the tentorium and the region of the foramen magnum. All of these membranes were detached and removed. A catheter was passed down the cervical canal but met with considerable resistance all the way; this, together with the fact that no cerebrospinal fluid was obtained on lumbar puncture, suggested that the spinal subarachnoid space was undeveloped.

COMMENT

The cases herein described and those previously reported in the literature[1–7,12–14,16] demonstrate that the Dandy-Walker syndrome has a well differentiated and established pathogenesis.

The cause of the malformation is delayed opening, or absence of, the foramina of Luschka and Magendie. This produces primarily an enlargement of the fourth ventricle, which, like a huge cyst or sac formation attached at the caudal end of the cerebellum, may fill the greater part of the posterior fossa.[1,14] This in turn interferes with the development of the cerebellum and prevents the migration of the transverse and confluent sinuses. These sinuses retain their fetal position in the posterior parietal bones instead of migrating to the occipital bones.[14] The cerebellar hemispheres are underdeveloped, and the caudal end of the vermis is often either absent or rudimentary, as shown in both our cases.

The fourth ventricle is usually enclosed by an abnormal caudal membrane, which, microscopically, is composed of more than 1 layer.[7] The outer layer is arachnoid, continuous with the rest of the cerebellar arachnoid; the inner layer is ependyma, continuous with that of the fourth ventricle. In the middle layer is collagenous tissue, apparently the residue of the tela choroidea and glia. The foramen of Magendie is usually occluded by an ependymal diverticulum, a structure usually absent in man after the fourth fetal month. In other instances, no trace of the foramen of Magendie can be found. In some cases, the lateral recesses end blindly so that there are no foramina of Luschka. In a few instances, one or both foramina of Luschka may be patent and in such cases the hydrocephalus is partially of a communicating type.[7]

Taggart and Walker[14] and Gibson[7] believe that the primary cause of this typical deformity is failure of the foramen of Magendie to open during intrauterine life. According to Benda[1] the atresia of the foramen of Magendie is only a part of the syndrome; he believes this represents a rachyschisis due to either extrinsic agents interfering with fetal development or, occasionally, genetic factors. Recently, Gardner, Abdullah, and McCormack[6] expressed the opinion that, at least in adults, because of certain features common to the Arnold-Chiari malformation, Dandy-Walker syndrome, and syringomyelia, these clinical entities could be an expression of the same disease produced by a common cause—failure of the outlets of the fourth ventricle to develop normally in the rhomboid roof of the embryo.

Once the basic pathology of this condition is known, it should not be difficult to recognize its typical radiologic features. Clinically, in these children, one may observe that the shape of the head is characterized by a marked prominence of the occipital bones.[1,10]

Skull x-rays. Because of the enormous cystlike formation behind the cerebellum in utero, the transverse sinuses fail to descend to their normal position. It would be possible, then, especially in older children, to observe that the inion is elevated and the impressions of the transverse and straight sinuses are in the posterior parietal bones instead of being located in the occipital bones.[14] This single sign, when present, is sufficient to suggest the diagnosis of atresia of the foramina of Luschka and Mag-

endie. In age groups in which the impressions of the transverse sinuses are difficult to recognize, there are other radiologic signs that facilitate the recognition of this condition. In the AP projection, the bitemporal distance appears less marked than in other types of hydrocephalus. In some instances, this may be normal or even below the normal limits. The lateral skull view reveals a thinning of the lower occipital bones, and the posterior cranial fossa appears markedly enlarged. This sign may differentiate this type of hydrocephalus from the cases of occlusion at or above the level of the aqueduct, in which the posterior fossa is usually smaller than normal.

Since enlargement of the skull takes place primarily in the occipital region, the distance between the occiput and the ear is greatly increased and the skull is distinctly dolichocephalic.[1] The lambdoid suture, which is relatively the least separated in most other types of hydrocephalus, is apt to show considerable separation.[10]

In conclusion, the most striking feature in the skull x-rays in these children is the marked enlargement of the occipital region contrasting with the minor involvement of the anterior part of the skull and virtually no alteration in the orbital configuration.

Ventriculography reveals dilation of the whole ventricular system, but what is more remarkable and diagnostic is the dilation of the aqueduct communicating with a large cyst-like formation in the posterior fossa (Figs. 3, 4, 7, and 8). Such findings are not mimicked by any other lesion. The tentorium and the posterior temporal and occipital horns of the lateral ventricles are elevated (Figs. 3 and 7). The position of the transverse and straight sinuses appears higher than normal. The projection of the cyst of the posterior fossa into the upper cervical spinal canal may be seen in the upside-down position (Fig. 4). This is a finding considered by Matson[10] as pathognomonic for this condition.

If air studies planned in a suspected case of Dandy-Walker syndrome are not done through the anterior fontanel, it is desirable to place the bur holes for ventriculography higher than usual. Maloney[9] reported on 2 cases not diagnosed preoperatively, in which the bur holes for ventriculography fell just on the elevated transverse sinuses. In addition, on some neurosurgical services, ventriculography is frequently performed with inadequate amounts of air (bubble air studies) with the sole purpose of obtaining information on the approximate dimensions of the ventricles and thickness of the cortex. When this small quantity of air reaches the posterior fossa, it is insufficient to visualize completely the large cystic formation, and the part of it that is filled is interpreted as a dilated cisterna magna. Such an occurrence has been reported in some cases of Dandy-Walker syndrome.[15]

Dye studies. In some cases of Dandy-Walker syndrome, there is patency of one or both foramina of Luschka,[7] some degree of patency of the membranes over the dilated fourth ventricle,[6,17] or dialysis of cerebrospinal fluid through the membranes of the cyst.[14] For this reason, dye passes from the ventricular system to the lumbar subarachnoid spaces. Very likely, the true nature of such cases is often not recognized, and they are diagnosed as communicating hydrocephalus.

Sinus venography has been used by Ingraham and Matson[8] to demonstrate the elevated location of the torcula and the transverse sinuses by injection of 3 to 5 cc. of 35% Diodrast into the longitudinal sinus at the anterior fontanel.

Surgical treatment. The procedure of choice is a suboccipital craniectomy with as wide an excision of the cyst wall as possible. The arch of the atlas should always be removed to allow exposure and excision of the projection of the cyst into the cervical spinal canal. Meticulous hemostasis throughout the operation is also important, as any formation of postoperative adhesions will quickly cause recurrent obstruction of spinal fluid circulation.[10]

In some instances, excision of the posterior fossa cyst alone will not relieve hydrocephalus and a second shunting procedure has to be performed.[10] Matson[10] believes that, when an obstructive hydrocephalus is already severe at birth, the surface subarachnoid pathways do not have a chance to develop adequately to receive and pass along the fluid directed to them by surgery.

Satisfactory surgical results can be expected, however, in this type of lesion provided it is recognized early in life and properly treated.

SUMMARY

Atresia of the foramina of Luschka and Magendie (Dandy-Walker syndrome) in 2 male infants is reported. The pathogenesis of this malformation is briefly described. Particularly stressed are the radiologic aspects of the condition, which are considered to be pathognomonic and may help in the early recognition of the lesion and preoperative diagnosis. Skull x-rays reveal impressions of the lateral sinuses higher than usual, thinning and bulging of the bones of the posterior cranial fossa, and prominent separation of the lambdoid sutures, with minor involvement of the anterior part of the skull. Ventriculography shows symmetric hydrocephalus with dilation of the aqueduct, an extremely large cystlike formation in the posterior fossa, at times projection of this "cyst" into the upper cervical canal, and elevation of the tentorium and inferior portions of the lateral ventricles. Surgical indications are also considered.

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Effects of thiosemicarbazide on spinal reflex activity

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A NUMBER of reports indicate that many drugs of the hydrazide group are powerful convulsants.[1,2] Killam and Bain[3] and Roberts, Rothstein, and Baxter[4] have suggested, on the basis of both in vivo and in vitro studies, that this effect is due to interference with enzyme systems in the central nervous system that require pyridoxal as a coenzyme. Seizures produced by hydrazides are stopped by the administration of pyridoxine or pyridoxal. Evidence suggests that a drop in gamma-aminobutyric acid (GABA) levels in gray matter—as a consequence of blocking enzymatic decarboxylation of glutamic acid to GABA—might be responsible for the development of seizure activity, since topical application of GABA will stop hydrazide-induced seizures.[5] Additionally, GABA and convulsant hydrazides have opposite effects on potentials evoked in the mammalian cortex.[6]

The marked "inhibitory" action of GABA, a normally occurring constituent of mammalian brain, has been tested in crustacean stretch-receptor preparations and in the mammalian cortex. Whether it is an inhibitory transmitter, a blocking agent of excitatory synapses,[7] a regulator of neuronal excitability,[8] or a biochemical relative of a substance having one or more of these properties is still an unsolved question.[9]

Since GABA does not appear to cross the blood-brain barrier[4] when given intravenously unless radical procedures are employed to destroy the barrier first, we have employed parenterally given thiosemicarbazide (TSC), which Killam and Bain[1,3] have shown to lower GABA levels considerably in brain tissue. Our basic objective was to test the effects of TSC on various processes in the mammalian central nervous system, operationally defined as "inhibitory," and evaluate the role of GABA in them indirectly. It must be recognized, however, that the blockade by TSC of other pyridoxal-dependent enzymatic systems may be responsible for the effects of TSC.

This report deals with the effects of TSC on reflex inhibition in the cat spinal cord.

METHODS

Preparations were made in 3 ways.

1. Intact cats, either lightly anesthetized with pentobarbital or immobilized with gallamine triethiodide (Flaxedil) and kept under artificial ventilation, were used in this group. Local analgesia of painful areas was secured by procaine infiltration.

In these animals, bulbar reticular inhibition —of tendon jerks in the Nembutalized animals or of mono- and polysynaptic ventral root reflexes in the paralyzed animals—was used as the test situation.

2. Decerebrate cats, with midcollicular transection of the brain stem under ether anesthesia, were used in this group. Inhibition of decerebrate rigidity by bulbar reticular stimulation was the initial criterion. They were then immobilized and artificially ventilated. Laminectomy and dissection of hind-limb nerves and ventral roots were carried out. Mono- and polysynaptic ventral root reflex responses induced by peripheral nerve stimulation were obtained by oscillographic recording from the proximal end of cut ventral roots. Reticular inhibition of these reflex responses was the test situation in this group.

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This study was supported by U.S. Public Health Grant B-611.
Dr. Buchwald was aided by U.S. Public Health Service Senior Research Fellowship SF-196.

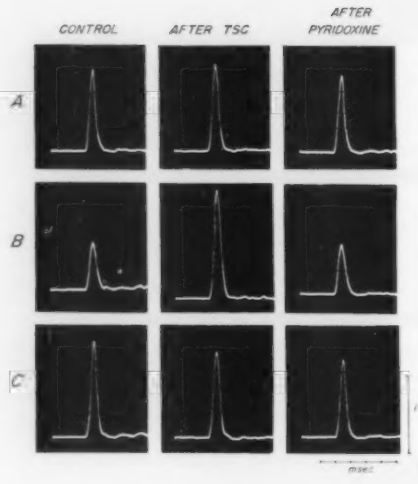

Fig. 1. Monosynaptic reflex (decerebrate cat) obtained by stimulating nerve to semitendinosus and recording from L7 ventral root. [A] Control responses. [B] During bulbar reticular stimulation. 100 cps at 3 v.= 0.02 msec. pulses. [C] After reticular stimulation. Vertical columns show records before drugs, two hours after 40 mg. per kilogram of TSC, and twenty minutes after 125 mg. of pyridoxine.

3. Spinal preparations were made, with the cord transected at midthoracic level one day before the acute experiments. In these, laminectomies and leg nerve dissections were carried out after local procainization. The changes induced by the drugs in the characteristics of the responses recorded from the ventral roots were assessed in this group.

In all cases, after establishment of the control conditions described above, TSC was given intravenously in a single dose of 30 to 50 mg. per kilogram. When the effects of the drug had been observed one and a half to two hours later, pyridoxine hydrochloride was given intravenously in a fixed dose of 125 mg. These amounts of drugs had proved adequate to produce generalized electrical and motor seizures in free-moving cats (TSC) and to stop these seizures (pyridoxine).

RESULTS

Reticular stimulation, which inhibited both tendon jerks and mono- and polysynaptic re-

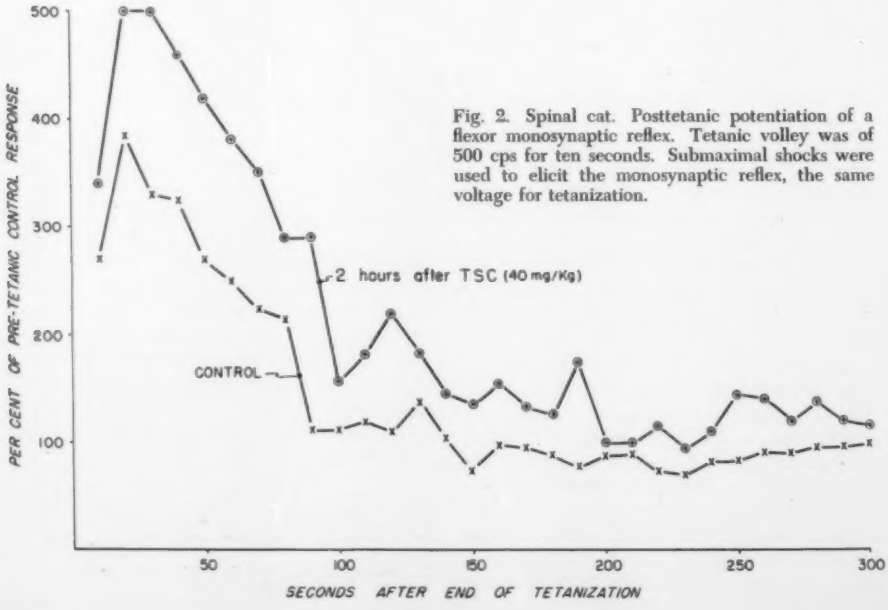

Fig. 2. Spinal cat. Posttetanic potentiation of a flexor monosynaptic reflex. Tetanic volley was of 500 cps for ten seconds. Submaximal shocks were used to elicit the monosynaptic reflex, the same voltage for tetanization.

flex responses in the first 2 groups of preparations, was no longer effective one and a half to two hours after TSC injection. The inhibitory effects of reticular stimulation were reestablished fifteen to thirty minutes after administration of pyridoxine (Fig. 1).

In all 3 types of preparations, the absolute amplitude of mono- and polysynaptic responses and the duration of the polysynaptic complex wave responses were enhanced by TSC and reduced to the control values after pyridoxine. Additionally, posttetanic potentiation of monosynaptic reflexes was increased by TSC administration (Fig. 2). This effect also was reversed by pyridoxine.

DISCUSSION

These data establish that the inhibitory effects of bulbar reticular stimulation are no longer observed after thiosemicarbazide injection. On the other hand, concomitant changes induced by this drug have been observed which indicate an increased level of excitability of spinal structures, since they occurred in spinal cats as well as in the other preparations. This could be interpreted in terms of depletion of an inhibitory transmitter substance—presumably GABA—with consequent reduction of inhibitory activity, either induced as in the case of reticular stimulation or acting in a continuing way, thus causing an enhancement in reflexes we observed. This interpretation would involve the assumption that reticular inhibition of spinal reflexes was mediated through the same mechanisms postulated by Eccles[10] for "direct inhibition," that is, the presence of inhibitory interneurons causing the generation of hyperpolarizing inhibitory postsynaptic potentials (IPSP) in motoneurons through an inhibitory transmitter agent.

Terzuolo, Sigg, and Killam[8] have shown that IPSP's could still be generated in anterior horn motoneurons in cats by reciprocal stimulation after dosages of thiosemicarbazide similar to those employed by us. Curtis and Watkins[11] have demonstrated that IPSP's can still be recorded from impaled spinal motoneurons after close electrophoretic injection of GABA. These 2 complementary observations seem to rule out quite conclusively the possibility of GABA being an inhibitory transmitter. Curtis and Watkins' data, showing that membrane potential was unaffected but membrane conductance was decreased by GABA in their experiments, back their conclusions regarding this substance as a regulator or "stabilizer" of membrane conductance without any demonstrable synaptic effects.

In view of these data, it is impossible for us to interpret our own experimental material in the terms suggested first. It would seem then that the seizure activity,[1,3] the enhanced evoked cortical responses,[6] and augmented mono- and polysynaptic cord reflexes following thiosemicarbazide administration can be explained by changes in membrane regulation caused by depletion of GABA. The opposite effects induced by blockade of GABA transamination by hydroxylamine[12] with consequent increases in endogenous GABA levels would strongly support the implication of this substance in the mechanisms of hydrazide action.

Unfortunately, the reasons why reticular inhibition of spinal reflexes could no longer be demonstrated after TSC administration are still not clearly understood. It is possible that the increase in cord excitability was such that only "masking" of inhibition occurred, but other mechanisms are also possible. The lack of direct evidence from intracellular recording during reticular inhibition, with measurement of membrane potential and conductance, makes any interpretation of this part of our data very difficult.

SUMMARY

1. Thiosemicarbazide has been found to cause an increase in the amplitude of spinal mono- and polysynaptic reflex responses. Bulbar reticular inhibition of these reflexes is no longer demonstrable after this drug is injected.

2. Pyridoxine reverses the above mentioned effects, leading to the conclusion that blockade of a pyridoxal-dependent enzymatic system by TSC is responsible for the electrophysiologic changes. Evidence is cited that suggests that this enzymatic system is involved in the metabolism of gamma-aminobutyric acid.

3. It is concluded that a result of thiosemicarbazide administration is an increase in the level of excitability of spinal structures, quite in agreement with its powerful convulsant effects.

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Determination of topologic human brain representations and modifications of signs and symptoms of some neurologic disorders by the use of high level ultrasound

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THOSE ASPECTS of high intensity, focused ultrasound which make it especially useful for elucidating and inducing changes in brain mechanisms subtending certain neurologic disorders and thus for modifying their clinical manifestations have resulted from extensive experimental animal studies carried out during the past decade by several of us (Messrs. Fry and associates). These studies, making use of precisely controlled dosages of ultrasound, have led to several initial discoveries and published reports that may be synopsized as follows:

1] Permanent lesions of arbitrarily predetermined size, shape, and orientation can be produced at any site(s) in the brain. No disruption of intervening tissue is thereby entailed.[1–5]

2] Changes in function of the tissues can be achieved by suitable modification of the parameters of irradiation. Such changes can be both short-lived ("reversible") and enduring ("irreversible").[6] The reversible changes need not be attended by histologically identifiable lesions.[7–10] Here again, intervening tissues regularly escape demonstrable disruption.

3] The vascular system can be left anatomically intact and functioning in cerebral regions in which all neuronal elements (neurocytes and/or their fiber processes) are destroyed.[1–5,11]

4] Fiber tracts of white matter can be interrupted without damage to neighboring or surrounding gray matter that receives an equal dose of ultrasound.[1,3,5,11,12]

5] Mortality and morbidity are extremely small if brain structures not directly involved in mediating vital functions and the responsive state ("consciousness") are not irradiated to produce enduring changes.

6] Evidence thus far obtained indicates that cumulative effects (comparable, for example, to those induced by x-rays and high energy particle radiation) are not produced.

7] Strong presumptive histologic evidence is at hand to indicate that differential susceptibilities to ultrasound exist, in addition to those cited in items 3 and 4. With appropriate choice of the parameters of irradiation, myelin sheaths appear more vulnerable than axis cylinders.

In consequence of these disclosures, it appeared feasible to employ ultrasonic procedures for investigating and modifying the mechanisms underlying certain neurologic disorders in man. Accordingly, we performed during the past one and one-half years 46 ultrasonic irradiation procedures on 41 patients. The disorders to which our attention has been directed are:

Hyperkinesia, the patterned tremors in park-

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Paper presented with motion picture illustration at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 18, 1959.

Partially supported by grants from the Parkinsons Disease Foundation, the Easter Seal Research Foundation, and by Grant B1955 with the Institute of Neurological Diseases and Blindness, National Insttutes of Health, U. S. Public Health Service.

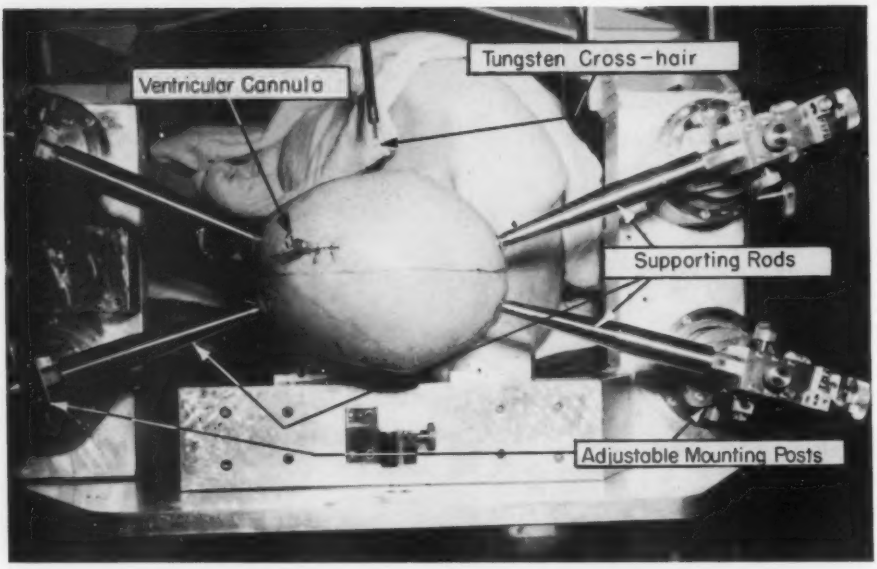

Fig. 1. Close-up of patient mounted in the head holder. The 4 supporting rods (by which the cranium is held rigidly in position) and their corresponding adjustable mounting holders or posts are also illustrated. See the text description of Figure 2 for information on the tungsten crosshair.

insonian patients and the nonpatterned, abnormal movements in cerebral palsied and dystonic patients

Hypertonus, the sustained, usually progressive rigidity in parkinsonian patients and the fluctuating, relatively nonprogressive rigidity ("tension") in athetotic and dystonic patients

Bradykinesia, micrographia, and deficient automatic associated movements in parkinsonism and certain other disorders

Intractable pain—phantom limb and stump pains in amputees, thalamic pain (Déjèrine's syndrome), and the pain of postherpes zoster

Hyperalgesia, hyperesthesia, paresthesias, and dysesthesias in or neighboring upon regions afflicted by amputation stump, thalamic, and postherpetic pains

Phantom limb image in amputees

TECHNIC

Geometric distributions of various brain structures (or parts thereof), the disruption of which modifies the signs and symptoms of the disorders listed above, are determined by placing a number of selective ultrasonic lesions in each patient's brain. The conscious patient cooperates for "objective" neurologic examinations and verbal interviews during and after the production of a lesion at each position.

The technic employed in our first 40 human cases has been described in previous publications.[10,13,14] Experience with these early cases suggested certain advantages that might be gained by revising our original modus operandi. Such revisions have recently been implemented. The technic currently in use and the reasons that prompted adoption of departures from the original may be briefly summarized as follows:

As previously, the reclining position is used to expose the lateral aspect of the patient's head. The cranium is held rigidly by 4 stainless steel rods, the rounded tips of which engage superficial "dimples" (hemispheric tipped indentations 0.5 mm. in diameter and 2.5 to 3 mm. in depth) drilled in the outer table and diploe via short incisions in the scalp (Fig. 1). Each rod is clamped in an adjustable holder by

a device that permits micrometric determination and, later, reduplication of its position in space.

After the patient's head is firmly secured by the rods, lateral and longitudinal (A-P or P-A) cranial roentgenograms are made with radiopaque material (colloidal thorium dioxide 25%, 3 cc.) mixed with the cerebrospinal fluid in the ventricles. The brain coordinate landmarks provided by the lateral ventriculogram are the ventricular boundaries of the anterior and posterior commissures. The landmark provided by the longitudinal ventriculogram is the midline of the third ventricle. The x-ray tubes for obtaining the lateral and longitudinal ventriculograms and their corresponding cassettes are mounted in reproducible positions on the head holder (Fig. 2).

The positioning system seen in the central part of Figure 2 supports and moves a tungsten cross hair (embedded in a plastic rod). The images of this cross hair appear on the ventriculograms and are used in the determination of the coordinates of the brain site(s) to be irradiated. Coordinate lines are drawn on the films, and measurements of the projected images of the commissural landmarks, midline of the third ventricle, and tungsten cross hair are made. The tungsten cross hair referred to replaces the tapered metal rod pointer used in the earlier technic, upon which we have reported.[10,13]

In the original technic, the patient was removed from the head holder after the ventriculograms were made. He was then brought back at a later time (but not sooner than four or five days) and repositioned in the head holder for reflection of a lateral scalp flap, craniectomy, and ultrasonic irradiation. Immediately after irradiation (unilaterally or bilaterally, as desired), the bone flap was replaced and scalp closure effected.

In this method, 3 serious disadvantages inhere. First, if any repetition and/or extension of irradiation should subsequently be indicated, reelevation of scalp and bone flaps would be required. Second, the patient about to undergo a period of ultrasonic irradiation (for which his sustained cooperation is a necessary precondition) is required to endure the physiologic and psychologic stresses related to reflection of scalp and bone flaps. Third, while many clinical changes manifest themselves either immediately or within a period of minutes to an hour or two following exposure at an array of positions, other changes require several days or even months for their evolution. For example, in some parkinsonian patients tremor and/or rigidity may be completely abolished on the operating table only to return to some degree within a few days, weeks, or months after irradiation. A similar circumstance may occur in patients subjected to operation for relief of intractable pain.

For all these reasons, it appeared desirable to devise a procedure to eliminate the disadvantages mentioned. Such has been accomplished by irradiating through the intact skin in patients from whom an appropriate bone flap has been removed at some convenient time prior to implementing ultrasonic irradiation.[15] At the time of removal of the bone flap, ventriculography is performed during general anesthesia. The patient's head is secured, as previously described, in the head holder. Immediately following ventriculography, the scalp flap is elevated and the bone flap removed and stored for later replacement. A thin sheet of polyethylene may be inserted to prevent the formation of adhesions between scalp and dura. The scalp is then sutured and a plaster dressing applied. Where desirable, a light,

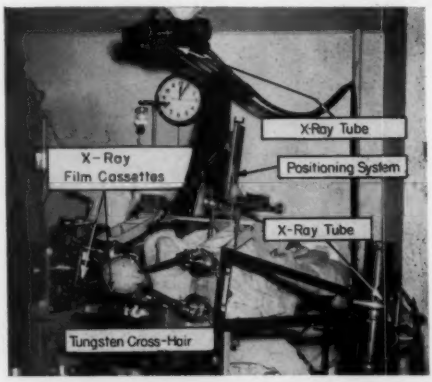

Fig. 2. The patient mounted in the head holder. The x-ray tubes and film cassettes, the positioning system which supports and moves the tungsten crosshair, and the crosshair are illustrated.

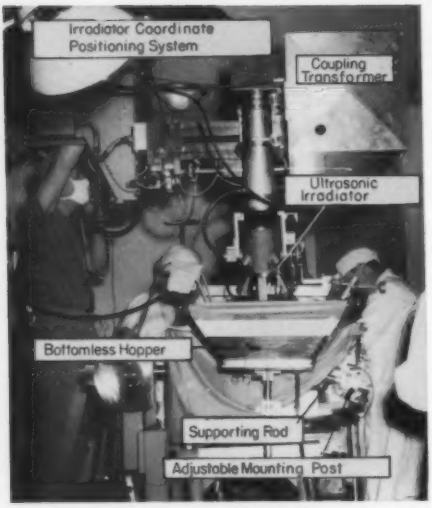

Fig. 3. Arrangement of patient, head holder, hopper, ultrasonic irradiator (shown partially immersed in degassed saline within hopper), and irradiator coordinate positioning system for implementing high level focused ultrasonic irradiation of an array of sites in the brain. Irradiation through the *intact* skin is being carried out. (The coupling transformer, mounted on the irradiator positioning system, permits electrical matching of the irradiator load to the electronic driver.)

fiberglass helmet can be furnished to provide protection.

At some convenient time after scalp healing has taken place, the patient, now in a fresh state, is repositioned in the head holder. To this end, the short, healed scalp incisions in the forehead and occipitoparietal regions are reopened during local anesthesia for admission of the supporting rods. Ultrasonic irradiation can now be effected through the intact scalp. ***This procedure can be repeated*** with a minimum of inconvenience ***as often thereafter as is desired.***

The procedure originally described—that of employing a bottomless "pan" or hopper for supporting the degassed saline through which the ultrasonic beams are transmitted from source to tissue—has been retained in principle with the following important technical modification. A water-tight seal between hopper and skin surface is accomplished by means of a pneumatic gasket that avoids suturing of the scalp to pan. If the skin incisions permitting access of the supporting rod tips to the 4 cranial "dimples" are suitably protected, the procedure described can be conveniently accomplished without the necessity of resorting to aseptic-sterile technics (Fig. 3).

Ultrasonic irradiation is now accomplished at a suitable array of sites within or on the boundaries of one or several brain structures determined by [1] subjective and objective changes arising during the irradiation sequence on the patient and [2] experiences accumulated from previous procedures on other patients. Following each individual "exposure," subjective and objective neurologic and psychologic tests are carried out. The patient's performances are recorded and, in appropriate instances, are documented in the form of motion picture and sound tape recordings. In such circumstances, the patient remains in good condition—alert, clear, cooperative, and able to help himself from the operating table at the termination of the procedure.

A period of postoperative observation follows each irradiation procedure. Long-term changes are evaluated with a view to deciding whether additional irradiation is indicated. After the patient has been followed clinically for a sufficient period of time to indicate that such favorable changes as have been brought about are relatively sustained, the patient's bone flap can be replaced as a free graft or, if preferred, an acrylic plate may be substituted for it.

CEREBRAL STRUCTURES CURRENTLY UNDER INVESTIGATION

The clinical results obtained in the first 12 cases have been reported upon in detail[13] and will not be reiterated here. It is not within the scope of the present paper to synopsize the results obtained in 30 subsequent cases subjected to ultrasonic irradiation. Such will be made the basis of a separate report. Our intention here is, rather, to cite those cerebral structures, certain parts and/or boundaries of which have been made ultrasonic target regions, and to describe certain of the physiologic and psychologic effects arising from their irradiation.

In the first patients manifesting the tremor and rigidity of Parkinson's disease, the arrays of sites at which the common focus of the

ultrasonic beams was directed corresponded to the region of the ansa lenticularis medial and ventral to the medial segment of the globus pallidus. This procedure proved in some patients insufficient to relieve all tremor and rigidity of the contralateral limb(s). Moreover, the proximity of certain nuclei of the hypothalamus, optic tract, and genu of the internal capsule to the pallidofugal complex invited untoward complications.[13] A search was therefore instituted for other structures in which an array of ultrasonic lesions might prove effective for favorably modifying tremors and rigidity, economical in respect of the volume of tissue required to be irradiated, and "safe" as regards the advent of unintended neurologic deficits. Portions of the following structures were selected for irradiation because they are known anatomically to be related to the pallidofugal complex: the posterior part of the substantia nigra and/or its superior medial border; the base of the ventrolateral nucleus of the thalamus; the tegmental field of Forel; the zona incerta; and the fiber tract regions, H_1 and H_2.

In these structures, it has been possible to exhibit spatial distributions of neural components, irradiation of which results in the modification of tremor and/or rigidity in various muscle groups of the body. Of course, much further work is required to establish the details of these distributions. However, from the data now at hand, it is apparent that tremor and rigidity are not necessarily simultaneously modified, although in some cases they have proved to be so.

Our data indicate that an anterior-posterior topologic distribution of neural elements, corresponding to groups of muscles of the head, neck, upper limbs, trunk, and lower limbs, respectively, primarily involved in the mechanism of rigidity but also entering into the mechanism of tremor is present in the basal part of the ventrolateral nucleus of the thalamus and that a similar distribution, involved primarily in the mechanism of tremor, is present along the border of the posterior part of the substantia nigra.

In addition to irradiating the above-named structures in cases of parkinsonism, we have irradiated them in cases of athetotic cerebral palsy, dystonia musculorum deformans, and other variants of nonpatterned hyperkinesia which, up to the present, have not been given a formal clinical designation.

Patients manifesting various types of chronic intractable pain have also been subjected to ultrasonic radiation directed at sites within and/or on the boundaries of various structures of the dorsal thalamus, namely, the ventroposterolateral, ventroposteromedial, central median, dorsomedial, and lateral posterior nuclei. The types of cases studied in this way have included amputation stump, phantom, thalamic (Déjèrine's), and postherpetic pains.

The first patient presented amputation stump and phantom pain as well as a phantom image of the right upper limb. Unilateral irradiation directed at sites in the ventroposterolateral nucleus of the thalamus was employed. During operation, the stump and phantom pains were eliminated and remained in abeyance for approximately three months. Similarly, the phantom image and dysesthesias in the stump were eliminated at the time of irradiation, only to recur with the return of the pain in the stump.

In this patient, some neurologic deficits in the lower limb and trunk ipsilateral to the amputation stump were produced (hypalgesia, hypesthesia, pallhypesthesia, and partial acragnosis). During the fifth postoperative week, the patient noted the development of a "sunburn-like" discomfort of the right cheek. This rapidly spread to involve the remainder of the right side of the body. The "sunburning" subsequently assumed the character of a typical thalamic (Déjèrine's) syndrome.

Because of the recurrence of the original symptoms and the development of thalamic pain in this patient, a more medial irradiation was carried out on a second case of amputation stump and phantom pain with phantom image of the left upper limb. The patient was completely relieved of pain in the stump and phantom, of tenderness and dysesthesias in the stump, and of the phantom image. He exhibited no postoperative sensory, motor, coordinative, or psychologic deficit. The original symptoms began to recur in about eight weeks and became troublesome during the fourth postoperative month. Up to the present time, no symptoms suggestive of thalamic pain have been described by this patient.

In the first case of Déjèrine's syndrome sub-

jected to ultrasonic irradiation directed at sites in the medial part of the ventroposterolateral and ventroposteromedial nuclei, no favorable or unfavorable modification of the thalamic pains and dysesthesias ensued. However, when, in a second patient suffering from thalamic pain, the common focus of the ultrasonic beams was directed at the basal-lateral part of the border region of the centromedian nucleus, the pains and dysesthesias were completely eliminated during and after operation for several weeks. No neurologic deficit was demonstrable. As in the previously mentioned cases with amputation stump pain and phantom image, this patient reported a partial recurrence of symptoms during the eighth postoperative week. Within another month, they had virtually returned to their preoperative status.

A similar irradiation array to that just described was employed for the relief of severe postherpetic pain, dysesthesias, paresthesias, and tenderness in the distribution of the right ophthalmic division of the trigeminal nerve in a male, aged 70 years. Here again, the discomfort was completely relieved, without imposing further neurologic dysfunction, during the operation. Unfortunately, the patient's symptoms recurred during the sixth postoperative week. The patient reported that only one feature of his preoperative discomfort—a transient sporadic lancinating pain—had not recurred.

A parkinsonian patient died on the fifth postoperative day and another on the seventh. In the first of these, a bilateral pneumonitis and, in the second, complications consequent upon a severely toxic gastroenteritis were revealed at autopsy. In both instances, the patients remained relatively unresponsive during the postoperative period. From the standpoint of achieving a favorable modification of rigidity and tremor, both patients were considered during operation as likely to make appreciable therapeutic gains.

DISCUSSION

The high intensity ultrasonic method of producing selective, arbitrarily shaped arrays of lesions in the nervous system constitutes a more versatile tool than any heretofore employed for studying neural functions and dysfunctions. Looking toward the development of new and/or improved methods for the alleviation of various neurologic and psychologic disorders, it became apparent to us that, in the endeavor to achieve optimal benefit for the greatest number of patients, the use of the ultrasonic tool might be most fruitfully implemented by first employing it to elucidate the pathogenetic mechanisms basic to these disorders. This objective has entailed and continues to entail irradiation of human brain structures, the detailed operations of which are as yet poorly understood. Consequently, the results obtained through the use of ultrasound may be evaluated by considering the extent to which data bearing on the pertinent neural mechanisms have been and are being acquired. In brief, the usefulness of focused ultrasound as a tool in human neurosurgery can be more meaningfully expressed in terms of the rapidity with which it yields information and the extent to which it renders results reproducible than in terms of raw percentages of favorable clinical cases. Indeed, it is at the present time evident that the criterion of "favorable clinical results" cannot provide a useful basis of evaluation, since uncorrelated data resulting from investigations of the functions of a *variety* of cerebral structures cannot be meaningfully grouped together until some unifying schema is evolved. Until the time essential to reaching such a schema has passed, the data resulting from disruption of each specific structure (or of parts and/or combinations thereof) must be considered separately. Obviously, once an irradiation array for obtaining a favorable clinical outcome has been identified and the results obtained by the use of the ultrasonic method have been established as reproducible, any desired number of favorable cases may be produced.

The process of deriving a substantial and predictive unifying schema for any sign (for example, hyperkinesia, akinesia, and hypertonus), symptom (pain, dysesthesias, and paresthesias) or syndrome (parkinsonism, thalamic pain) involves a good deal of systematic spadework at this, our present limited stage of knowledge. The manifest effects of arrays of lesions in target structures, taken singly and in various combinations, must be painstakingly observed, recorded, and later verified. Plan-

ful trial-and-error experimentation and prompt exploitation of newly acquired knowledge, both "positive" and "negative," appear essential to making rapid progress in this area of study.

As mentioned above, the ultrasonic method permits making arrays of lesions so positioned and oriented as to conform to specific neural structures or boundary regions thereof *without* adversely affecting intervening neural tissues. Up to the present, this has not proved possible with any method requiring mechanical penetration of tissues by conventional scalpel, leukotome, electrodes, or cannulas.

It is to be emphasized that the full potential of the ultrasonic method is not realized if the focus of the ultrasonic beam(s) is placed at a single "center" and the ultrasonic dosage parameters alone are employed to control the size of the resulting lesion. The principle just mentioned, that of controlling the size of the lesion from a single "center" by varying the pertinent parameters (for example, time and current in electrocoagulation or quantity of necrotizing agent in chemocoagulation), is of necessity currently employed by methods involving mechanically penetrating instruments.

Finally, in evaluating the ultrasonic method as applied to basic and clinical neurologic problems, one must distinguish on the one hand between *geometric accuracy* of positioning the focus at a site in the space occupied by the brain within the skull and, on the other, *anatomic accuracy* of placement in a specific site in some cerebral structure of interest. The geometric accuracy now realizable appears adequate for any studies we now contemplate. Refraction at the saline-dura interface can result in a 0.5 mm. shift of the focal region lateral to the beam axis if the ultrasound is focused at the greatest depths (10 to 12 cm.) in a human brain and if the angle of incidence is 45°. Smaller angles of incidence result in correspondingly smaller shifts, and, in any case, the irradiator coordinates can be adjusted to correct for the major part of shifts of the focal region resulting from refraction at the saline-dura interface. Anatomic accuracy, on the other hand, is limited by the precision and imprecision of currently available atlases. It may be reasonably anticipated that brain atlases and associated landmarking schemes will continue to be improved, thus enhancing in the foreseeable future the accuracy of human brain stereotaxy.

Since it is now possible to induce reversible changes in neural function(s) by the use of ultrasound, the investigator is fortunately not forced to await the improvement of atlases in order to improve the accuracy of anatomic positioning. In fact, by employing reversible dosages of ultrasound, he stands in a favorable way to contribute basic knowledge in this area. In addition, the construction of a more detailed 3-dimensional model of basic brain functions becomes feasible. Some useful work in this area has already been accomplished.[7–10]

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Apoplectic death due to intracerebral hemorrhage

An anatomic study

John S. Marks, M.D.

INTRACEREBRAL HEMORRHAGE is one of the most commonly encountered neurologic disorders; it was found in 7.5% of brain autopsies performed at the Philadelphia General Hospital during the period of this study and occurred in 3% of all autopsies on persons in the 30 to 80 age group. With an increasing geriatric population, better understanding of the pathophysiology of this condition is becoming important. There are relatively few reports in the recent literature, however, dealing with the anatomic features of this disease. As pointed out by Adams and vander Eecken,[1] the main clinical and pathologic characteristics of brain hemorrhage were described in the nineteenth century, but, in the light of recent advances in medical knowledge, many aspects remain unexplained. The studies of Aring and Merritt[2] in 1935, Hicks and Black[3] in 1949, and Wilson and associates[4] in 1951 are not primarily concerned with the pathologic anatomy of the condition. It was thought worthwhile, therefore, to review the fatal cases of cerebral hemorrhage seen at the Philadelphia General Hospital.

This study is based on 253 cases of massive supratentorial intracerebral hemorrhage studied in the laboratory of neuropathology at the Philadelphia General Hospital from January 1948 to October 1958. In accordance with the criteria established by Dorothy Russell,[5] lesions included were greater than 3 cm. in diameter in all instances. Intracerebral hemorrhages associated with trauma, blood dyscrasia, surgical intervention, ruptured aneurysm, subacute bacterial endocarditis, or other complicating factors were excluded from the study, as were instances of hemorrhagic infarction. In view of the composition of the patient population of this hospital, the series probably comprises a representative cross section of persons subject to the condition.

STATISTICS

The youngest patient included in the series was 34, the oldest 87. The peak incidence was in the seventh decade, but 123 (49%) of the patients developed intracerebral hemorrhage before the age of 60. The relatively low ratio of white to nonwhite (90:163) persons probably is not significant in view of the high percentage of Negro patients in the hospital population. No difference in sex ratio was noted, although the proportion of young Negro females was greater than might be expected.

ANATOMIC LOCATION OF LESIONS

Contrary to the generally accepted view that intracerebral hemorrhage results from rupture of large arteries, all lesions were located in the terminal fields of supply of cortical or ganglionic vessels, or both. Hemorrhage rarely involved the entire distribution of cortical arteries, but lesions in the basal nuclei frequently covered areas supplied by more than one ganglionic artery.

For this study lesions were classified according to the location of the most extensive tissue destruction without strict regard for anatomic boundaries. Minor degrees of overlap were disregarded. Hemorrhages were confined to the basal ganglia region in 116 (45.8%) and to the centrum semiovale in 85 (33.6%). Hemorrhages involved both basal ganglia and centrum semiovale in 52 (20.6%).

From the Laboratory of Neuropathology, Philadelphia General Hospital.

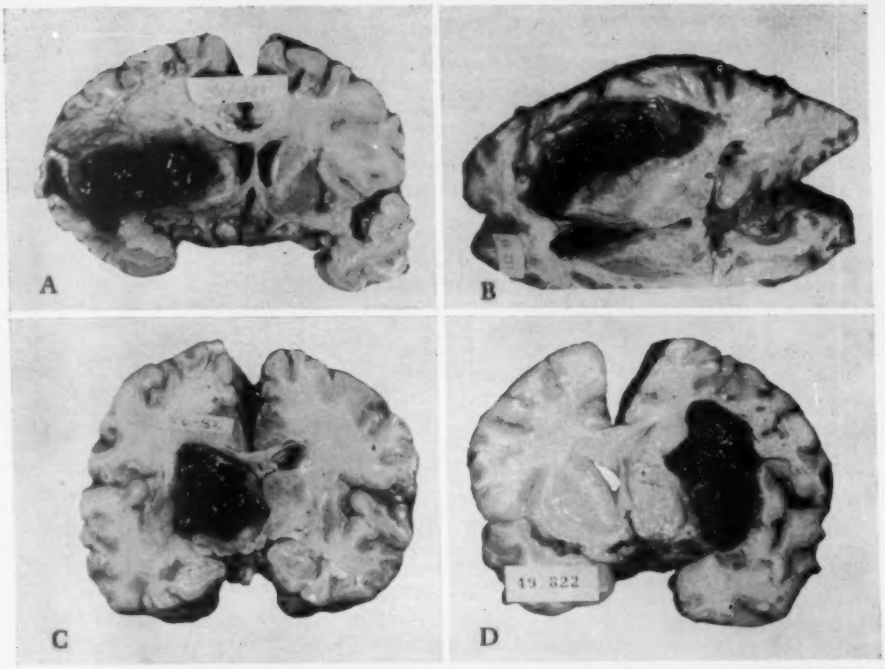

Fig. 1. Locations of intracerebral hemorrhage. [A] Involving both centrum semiovale and basal ganglia region. [B] In centrum semiovale rupturing into ventricle at "storm angle." [C] Hemorrhage confined to basal ganglia region. [D] Hemorrhage localized in centrum semiovale.

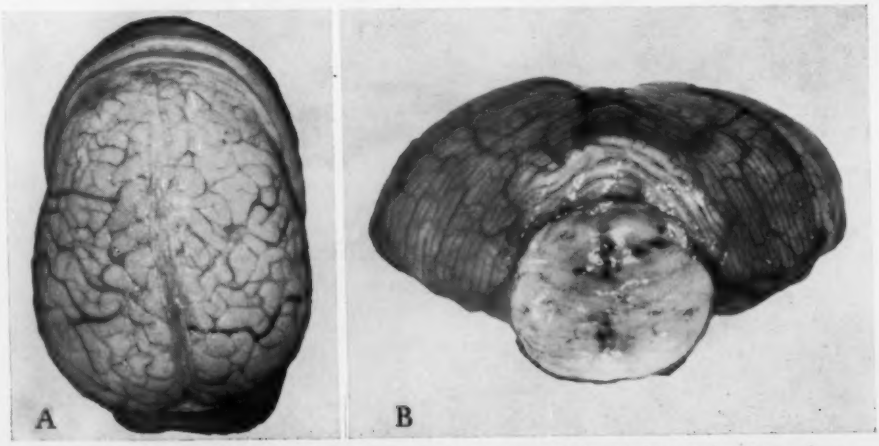

Fig. 2. Manifestations of increased intracranial pressure associated with intracerebral hemorrhage. [A] Flattening of gyri and narrowing or obliteration of sulci. [B] Secondary hemorrhages into brain stem.

INTRAVENTRICULAR RUPTURE

Extension of bleeding into the ventricles, a frequent complication of intracerebral hemorrhage, occurred in 160 cases in this series (63%). Contiguity of the hemorrhage within brain tissue to the ventricular cavity was apparently a factor in its development. In 78% of cases of intraventricular bleeding, hemorrhage involving the basal ganglia was associated. In the remaining cases, where the primary lesion was located within the centrum semiovale, rupture occurred through the anterolateral ventricular wall ("storm angle").

CAUSES OF DEATH

During the period covered by this study, no instance of massive intracerebral hemorrhage with a survival period longer than 6 weeks was found in cases coming to necropsy. The mechanism of fatal outcome is somewhat obscure, since destruction of the areas commonly involved is not physiologically incompatible with life. Rupture of the hemorrhage into the ventricular system is apparently one factor influencing the fatal outcome. One hundred fifty-four (96%) of the patients with this complication died within one week of the ictus. Since, however, almost half of those (40%) without intraventricular bleeding also succumbed within the same period, other conditions must also contribute. Death in a certain percentage must be attributed to visceral complications such as pneumonia, circulatory insufficiency, and metabolic imbalance. Where there is a rapid downhill course, with death within 3 days, the outcome would appear to be primarily related to intracranial factors. One hundred sixty (63%) cases in this series fall into this category. Characteristically in these cases the brain presented evidence of a severe degree of increased intracranial pressure. At least 2 of the following manifestations of this condition were present: [1] flattening of gyri with narrowing or obliteration of sulci; [2] herniation of the cerebellar tonsils; [3] herniation of the medial portion of one or both temporal lobes; and [4] presence of secondary petechial hemorrhage in the midbrain and upper pons.

In view of the potential relation of secondary brain stem bleeding to rapidly fatal outcome, its incidence appears significant. Its presence could be demonstrated in 30% of the entire series but was limited to those dying within 3 days after ictus. In this latter group, 76 (47%) had secondary hemorrhages into the midbrain and pons. This figure assumes particular importance in view of the fact that Poppen and associates[6] reported this complication in only 14% of a series of 258 fatal cases of supratentorial brain tumor, although not all were followed to post mortem.

The mechanism responsible for intracranial hypertension sufficient to result in bleeding into the brain stem in intracerebral hemorrhage is not entirely clear. Obstruction of cerebrospinal fluid outflow by intraventricular clots must be considered, since bleeding into the ventricles occurred in 80% of the rapidly fatal cases. However, the incidence of brain stem hemorrhage was no higher in the presence of this complication than in those persons dying within the same period without intraventricular rupture. The space-taking effect of rapidly expanding hemorrhage into the cerebral substance may also influence the development of secondary brain stem hemorrhage. It should be noted, however, that similar lesions may develop with massive supratentorial infarction unassociated with hemorrhage. During this survey, 17 such cases were observed.

SUMMARY

An anatomic study was made of 253 cases of uncomplicated intracerebral hemorrhage. Rapidly fatal cases were characterized by increased intracranial pressure, the most striking manifestation of which was secondary petechial hemorrhages into the brain stem. These were found in 47% of all patients dying within three days.

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Intramedullary spinal cord metastasis

D. Frank Benson, M.D.

WHILE THE SPREAD of tumor to the vertebrae and epidural tissues is commonly recognized and described, the dissemination of metastatic malignancy to the substance of the spinal cord has been considered a very rare occurrence. Many standard references either fail to describe or only briefly mention intramedullary cord metastases, and works dealing with spinal tumors,[5] metastatic tumors,[11] and neuropathology[8] imply that metastatic lesions in the substance of the cord are quite unusual.

The discovery of 3 cases with secondary cord deposits within a period of eight months suggests that the condition may not be as rare as described. We wish to draw attention to the clinical features presented by these cases and the cases reported in the literature.

Case 1. F. A., a 59-year-old white male, was admitted to the Veterans Administration Hospital, San Francisco, on June 21, 1958, with the chief complaint of weakness of both legs.

The pertinent history started in 1949, when a diagnosis of pernicious anemia was made. There was good response to therapy, but, when this was discontinued, there was a relapse marked by lemon-yellow skin, weakness, reduced vibratory and position sense, absence of deep reflexes in the legs and numbness and tingling of the legs. Vitamin B_{12} injections readily reversed this condition.

In April 1953, the patient was first admitted for investigation of an axillary mass, generalized lymphadenopathy, and splenomegaly. Biopsy revealed a poorly differentiated sarcoma resembling Hodgkin's disease. Treatment with nitrogen mustard and radiation reduced the nodes.

He was next admitted in June 1957 because of persistent cough. X-rays revealed a wedge-shaped density in the right hilum. Biopsy showed an epidermoid carcinoma, and a right pneumonectomy was performed.

The next admission was in January 1958 because of weakness of the right leg for a period of three weeks. On examination, a partial Brown-Séquard syndrome was demonstrable, with loss of pain and temperature sensation in the left leg and extensor toe signs on the right. The spinal fluid was normal, with a protein content of 36 mg. per cent. X-rays of the spine were entirely normal. A myelogram was performed and was considered entirely negative. The patient was given massive doses of vitamins and crude liver extract, and there was a definite improvement. He was discharged home and remained essentially well until about three weeks before his last admission, at which time he noted progressive weakness in both legs.

On admission, the general physical examination revealed a husky male with a large right thoracotomy scar; the spleen was down 2 fingerbreadths. Slight scoliosis to the righ and clubbing of all fingernails were noticed. The neurologic examination showed an alert, oriented patient who was unable to stand because of weakness of both legs. There was no weakness of the upper extremities. All of the deep tendon reflexes were hypoactive, and both ankle jerks were absent. Bilateral extensor toe signs were present. The superficial abdominal reflexes were absent. There was depressed perception to all sensory modalities in the lower extremities and lower trunk, but no clear-cut level could be ascertained. Urinalysis revealed a +3 sugar, and the fasting blood sugar was 168 mg. per cent, suggesting the presence of diabetes mellitus.

In the first three days of hospitalization, the patient lost all movement in the legs. A myelogram was performed six days after admission. The cerebrospinal fluid was at that time yellow, and Queckenstedt testing produced a slow rise and a slow fall. The myelogram itself showed no obstruction or filling defect in either the lumbar or thoracic areas. A full course of nitrogen mustard therapy was given but produced no change in the paraplegic condition. By this time, a sharp sensory level at T9 was evident.

The patient's hospital course was marked by a steady downward course and, in the final week, was complicated by the presence of a mild jaundice and a bout of pulmonary edema. He died on July 11, 1958.

At autopsy, a mass 3 x 3 x 1 cm. was found in the right posterior fossa. This mass was adherent to the dura and had invaded the substance of the cerebellum. Another smaller tumor was present within the substance of the cerebellum. The spinal cord contained a large number of tumors, all of which were located on the posterior and lateral aspects of the cord and none of which showed any connection to the dura. The largest of these measured 0.6 x 0.4 x 0.3 cm. and was located on

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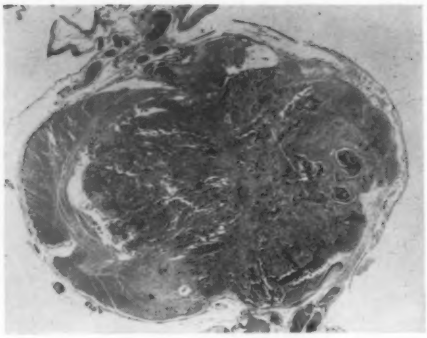

Fig. 1. *Case 1.* Cross section of spinal cord at T6 level. Hematoxylin-eosin stain.

the right posterior aspect of the T6 segment of the cord (Fig. 1). The dura stripped away from the cord readily, and there was no evidence of extradural metastasis.

The remainder of the necropsy, including careful scrutiny of the remaining lung, heart, lymph nodes, spleen, liver, and other organs, failed to reveal any evidence of tumor.

Histologic examination of the tumor masses revealed epidermoid carcinoma, which was of a pattern similar to that seen in the biopsy material from the pneumonectomy performed in 1957. The marrow was anaplastic, and there was no evidence of lymphoma or sarcoma in the lymph nodes or spleen. The pancreas showed fibrotic changes in the islands of Langerhans.

Discussion. The metastatic lesion at the T6 level will explain the initial Brown-Séquard syndrome and the later occurrence of paraplegia with a T9 sensory level. The presence of many tumors on the surface of the spinal cord but without connections to the dura suggests the possibility that they were seeded from the larger posterior fossa metastasis through the subarachnoid channels.

Case 2. L. G., a 58-year-old Chinese-American, had a cervical node biopsy in April 1958, at which time a diagnosis of metastatic pulmonary carcinoma with primary in the right midlung field was made. X-ray therapy was given to the right chest and supraclavicular areas. He remained asymptomatic until approximately June 1, 1958, at which time he began to notice numbness of the lower calves and feet. He next noticed some weakness of the legs and occasional cramps in the calves. Soon he complained of "buckling" of the knees and became unable to walk because of sensory loss and weakness of the legs. At this time, he felt that he was unable to empty his bladder completely.

He was admitted to Stanford University Hospital on June 17, 1958, at which time the general physical examination was essentially negative except for some pigmentation over the right chest. The neurologic examination revealed no abnormality in the cranial nerves, cerebellar functions, or upper extremities. There was weakness of the glutei, hamstrings, quadriceps, and all of the calf muscles, with total paralysis of the peronei and toe extensors bilaterally. Quadriceps and gastrocnemius reflexes were absent, and there was no toe movement with plantar stimulation. Sensory examination revealed analgesia of the feet and ankles to about midcalf in a stocking distribution and definite hypalgesia around the anus. Sphincter tone was noted to be poor. The bladder was distended, and, when the patient was catheterized, 900 cc. of urine was removed.

X-ray examination of the lumbar spine showed no abnormality. Lumbar puncture produced clear, colorless cerebrospinal fluid with an initial pressure of 210 mm. and quick responses to jugular compression. There were no cells, and the protein content was 107 mg. per cent. A myelogram showed no block or abnormality along the entire spinal cord. The patient was started on a daily regimen of active and passive exercises but gradually grew weaker. Constipation developed, and daily enemas were initiated. An indwelling catheter was constantly needed. The spinal fluid was reexamined one week later, with the same results except that the protein content was 80 mg. per cent. A repeat myelogram was performed and again revealed no evidence of spinal canal obstruction. Detailed "spot film" examination of the lumbar area failed to show any abnormality. The leg pains progressed, and increasing amounts of opiates became necessary. Palliative radiation in a dose of 1,320 r was delivered to the lumbar and lower dorsal spinal region without evidence of improvement. The patient showed progressive leg weakness and a slowly rising sensory level. He was discharged by ambulance to his home on September 10, 1958. His condition remained stationary at home until the morning of September 26, 1958, when he had a sudden, severe headache, loss of conjugate deviation to the right, and right face and arm weakness and died within one hour.

At autopsy, a 3-cm. tumor mass was found in the apical portion of the right lower lobe of the lung. Metastases were found in the left lung, liver, both kidneys, right adrenal gland, fifth lumbar vertebra, and many lymph nodes. Central nervous system metastases were found in the left temporal lobe, left insula, and lumbosacral spinal cord. This last mass was large (0.8 x 0.6 x 0.3 cm.) and fusiform in shape, extending from the conus up to the lower lumbar cord (Fig. 2). Above this level, many beaded nodules were seen on the nerve roots in the upper lumbar and lower dorsal cord segments. There was retrograde de-

generation of the posterior columns above the level of this lesion (Fig. 3).

A very large intracerebral hematoma was present in the left temporal lobe, extending from the anterior tip of the temporal horn of the lateral ventricle back to the parietooccipital area. This was of recent origin, as were the focal hemorrhages seen in the upper brain stem, and explains the sudden death of the patient.

Microscopic examination revealed a typcial squamous cell carcinoma of the right lung with similar histologic picture seen in all the metastases, including the large lumbosacral mass. The beadlike nodules seen at the junction of the cord and nerve roots did not show this same tumor picture, and further histologic studies are in progress to determine their significance.

Discussion. The lumbosacral mass explains much of the original neurologic picture. It was assumed that the later clinical picture of paresthesias, muscle cramps, weakness, areflexia, and rising sensory level was due to carcinomatous neuropathy, but further investigation of the nature of the nodules on the nerve roots may not support this view.

Case 3. P. M., a 56-year-old white man, was reported to be in perfect health until January 17, 1959. At that time, the patient noted a sudden sharp pain in the lower back while doing heavy work. This pain radiated to both hips but was most intense in the low back and remained steady despite bed rest and analgesics. Four days after the onset of pain, he consulted a physician and was sent to a local hospital, where x-ray examination of the lumbosacral spine was reported to be normal. A lumbar puncture was performed and showed "no recordable pressure," white blood cell count of 70, and cerebrospinal fluid protein of 80 mg. per cent.

On January 23, the patient complained of leg weakness, and, the next day, acute urinary retention developed. At this time, he became unable to defecate without enema. He was transferred to Stanford University Hospital on January 30, 1959.

Examination at the time of admission revealed a well developed, thin paraplegic with severe back pain. A 2 x 1 cm. firm node was palpable in the left supraclavicular fossa. On neurologic examination, there was a loss of sensation in both lower extremities and the lower abdomen to the level of the umbilicus. The lower extremities were flaccid, and plantar responses were absent. Cremasteric reflexes were absent; upper superficial abdominal reflexes and upper extremity reflexes were brisk and equal. The anus was patulous.

A lumbar puncture revealed an opening pressure of 140 mm. of cerebrospinal fluid. Jugular compression resulted in a slow rise to 250 mm. and a slow fall to 145 mm. of pressure; 1,000 red and 120 white blood cells were present, and the protein content was 102 mg. per cent. Roentgenographic examination of the chest revealed a large lesion in the right hilum. A myelogram performed on the day of admission was interpreted as showing a partial block of the spinal canal by enlarged cord. This enlargement was located at the level of T9 to T12. Bronchoscopy failed to reveal any pathology, and lymph node biopsy of the right cervical mediastinal area did not show evidence of tumor. Finally, a needle biopsy of the right hilar mass was performed, and the pathologic diagnosis of squamous cell carcinoma of the lung was made.

Fig. 2. *Case* 2. Cross section of sacral spinal cord. Hematoxylin-eosin stain.

It was felt that the patient had a paraplegia secondary to bronchogenic carcinoma metastasis and that surgical intervention would not lead to improvement. The patient was returned to his local hospital for supportive care. A communica-

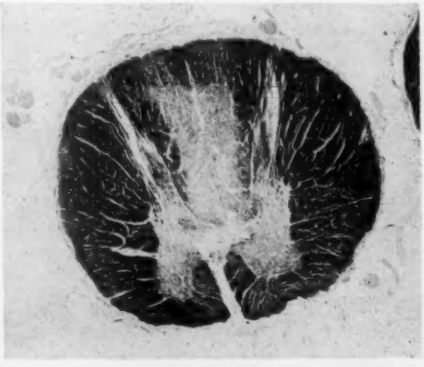

Fig. 3. *Case* 2. Section of cervical spinal cord showing retrograde degeneration. Weigert stain.

TABLE 1
CASES OF INTRAMEDULLARY METASTASES

Author and year reported	*Primary*	*Site(s) of metastasis*
Buchholz[11] (1898)	Breast	Multiple
Gallavarin & Varay[11] (1903)	Melanoma	Multiple
Taniguchi[11] (1904)	Lung	?
Pfungen[3] (1906)	Kidney	C2
Belz[11] (1912)	Kidney	Lumbosacral
Cary[11] (1913)	Chorioepithelioma	Lower cord
Sadelkow[3] (1918)	Lung	?
Nonne[11] (1923)	Lung	High cervical
Hilpert[11] (1926)	Lung	Thoracic (T1 & 2)
Simpson[11] (1929)	Lung	Lumbar
Roulet[11] (1929)	Melanoma	Cervical
Cirlo[11] (1930)	Lung	Lumbar
Hofheinz[11] (1931)	Breast	Thoracic
Haler[11] (1932)	Sarcoma of testicle	Multiple
Cantor & Stein[2] (1952)	Lung	Upper thoracic
Gaylord & Howie[6] (1938)	Kidney	Thoracic 8-9
Amyot & Laurin[3] (1939)	Breast	Lower thoracic
Wilson & Rupp[12] (1947)	Adrenal	?
Wilson & Rupp[12] (1947)	Melanoma	Cervical
Rash, Rosenbaum, & Heimburger[9] (1953)	Lung	Single large right sided tumor—From C2-D2
Sansoy[10] (1955)	Colon	Upper thoracic (T4)
Baron and Associates[2] (1959)	Lung	Single small lumbar
Baron and Associates[2] (1959)	Lung	Numerous, small, dorsal, lumbar, & sacral
Case 1	Lung	Lower thoracic with many smaller tumors
Case 2	Lung	Conus
Case 3	Lung	Lower thoracic

tion from this hospital informs us that he died March 4, 1959, and that permission for post-mortem examination was not granted.

Discussion. The diagnosis in this case has not been confirmed pathologically, but metastatasis to the spinal cord was suspected on the basis of the clinical and myelographic findings plus the presence of the large bronchogenic malignancy. The possibility that the cord lesion was secondary to a vascular accident of the cord was considered, but the progressive course of the paraplegia favored the presence of spinal cord metastasis.

INCIDENCE

The rarity of intramedullary spinal cord metastases is well documented by a review of the literature. Wilson[13] states that there were "... 7 or 8 cases known to 1930." Willis[11] gathered 12 cases in the literature up to 1932. Cantor and Stein[2] reported on 14 cases, including 1 of their own, in 1952. A review of the literature up to the present date produced 24 reported cases of intramedullary spinal cord metastasis (Table 1). This does not include the 3 cases presented in the paper.

The infrequency of intramedullary cord involvement contrasts sharply with the frequency of metastases to the vertebrae and extradural spaces. Elsberg,[5] Wilson and Rupp,[12] and Baron and associates[2] have all reported on large series of metastatic involvement of the spinal canal. Elsberg reports 254 cases of spinal cord involvement by tumor, 67 of which were meta-

static. All of the latter were extradural. Wilson and Rupp listed 53 cases of metastatic involvement of the spinal cord, 2 of which were intramedullary metastases. Baron and associates reviewed 127 cases of spinal cord involvement by metastatic disease and found only 2 with primary metastases to the substance of the cord. The combined statistics yielded a total of 247 cases of metastatic disease affecting the spinal cord with only 4 examples (1.6%) intramedullary lesions.

The spread of metastases to the vertebrae is recognized to be very common; Young and Funk[14] carefully studied the lumbar spine in 74 autopsies of patients with malignant disease and found evidence of lumbar vertebral involvement in 30 (41%). The majority of these were too small to be symptomatic, but this study points out the high frequency of involvement of the vertebrae in metastatic disease.

It is possible that the paucity of reported cases with intramedullary cord metastases represents a rather misleading picture. As Willis[11] states: "Metastatic growth in the spinal cord may be less rare than is supposed. This organ is seldom examined in routine necropsy work unless there have been clinical symptoms of disease in it and symptoms due to cord lesions may often be submerged by those due to coexisting cerebral lesions. In most cases with metastasis in the spinal cord, multiple cerebral metastasis is present as well." The 3 case histories in this report originally presented as perplexing spinal cord problems and did not give evidence of intracranial involvement until terminally. Necropsy interest was therefore centered on the spinal cord, but it is entirely possible that, had the cerebral symptoms occurred originally, the cord would not have been investigated. It seems possible that more frequent examination of the spinal cord at autopsy would show that intramedullary secondaries are not as rare as present statistics indicate.

TABLE 2

PRIMARY SITES OF INTRAMEDULLARY SPINAL CORD METASTASIS IN 24 CASES

Lung	10
(plus 3 cases in this report)	
Breast	3
Kidney	3
Melanoma	3
Adrenal	1
Hodgkin's Disease	1
Colon	1
Chorioepithelioma	1
Sarcoma of testicle	1

PATHOLOGY

The primary sites of the 24 reported cases of intramedullary spinal cord metastasis are listed in Table 2.

It will be seen that almost one-half of the verified cases resulted from primary lung tumors and the majority of these have been reported in the past seven years. In 1952, Cantor and Stein[3] found only 3 cases of intramedullary spinal cord metastases with primaries in the lung. This may represent further evidence of the increasing frequency of bronchogenic carcinoma,[1] but it may also suggest that lung tumors are more likely to spread to the spinal cord.

The pathologic picture has shown only minimal variation within the rather rigid criteria demanded by the term intramedullary. The tumors are located entirely within the substance of the cord and leptomeninges without involvement of the dura. In our 2 autopsy cases (Figs. 1 and 2) and those in the literature with illustrations,[3,10] the tumor has replaced most of the cord and distorted the remnants. Thus, it is impossible to prove that the origin was intramedullary and not from extramedullary intradural deposits, but, from the appearance of these histologic sections, the former appears probable. The location of the secondaries has ranged from the conus to the level of the second cervical segment with some preference for the middorsal region. Several cases[6,9] have been reported showing only a single discrete tumor, but most have had a large number of smaller tumors in addition to the large symptom-producing tumor.[2,4]

The histologic picture is similar to that seen in cerebral metastases with discrete tumor borders surrounded by an area of edema and compressed glial tissue. Severe anatomic distortion of the cord is caused by the tumor invasion, compression, and resulting vascular

insufficiency. Malacia of contiguous areas of the cord, both rostral and caudal to the lesion, plus ascending and descending retrograde degeneration of the cord, is common (Fig. 3).

Several routes of spread of tumor to the substance of the cord have been proposed, and it is suggested that, quite possibly, the route varies in different cases. Among the possible routes that have been suggested are:

1. Hematogenous spread from the lung, through the heart and arterial circulation to the cord. The pathologic picture in many cases would support this theory, especially when there are metastases spread through many organs.

2. Lymphatic course with tumor ascending through the perineural lymphatic system of the peripheral nerves to the subarachnoid space.

3. Spread through the vertebral vein system. This large system of valveless veins carrying blood under low pressure is subject to reversal of flow and could carry tumor cells to the cord (as well as to the dural sinuses of the brain). The tumor cells could enter this system by the azygos veins or through venous channels connecting an adrenal gland with the vertebral plexus. This would appear to be a satisfactory explanation for metastases found in the lumbar and sacral cord.

4. Embolic spread through the subarachnoid spaces. It is well established that tumors of the glioma series may spread by seeding through the cerebrospinal fluid[8] and it is quite logical that metastatic malignancy could do the same.

5. Direct involvement of the cord substance by extradural or dural tumors. This occurs frequently but is not included in this series because the primary metastatic site is obviously not intramedullary.

It is theoretically possible for tumor cells to reach the spinal cord by any of the first 4 methods, and there are possible examples of each in the literature. At present, there is insufficient evidence to select any 1 of these methods as the most common.

Another important consideration is why intramedullary metastasis is so rare in comparison to extradural metastasis. The cord has a rich vascular supply with numerous intercommunicating collateral vessels, but most of these vessels are of small caliber and may be less accessible to wandering tumor cells. Possibly, the paucity of lymphatic channels into the substance of the cord[7] offers some explanation. Whatever the reason, there can be no doubt that tumor cells metastasize to the substance of the cord much less frequently than they do to the extradural spinal structures.

CLINICAL PICTURE

The clinical picture of intramedullary metastatic growth is of sufficient consistency to warrant attention. The exact symptomatology will vary with the level of the metastasis, but, in essence, the intramedullary metastasis will show the same type of symptom progression as a similarly placed primary intramedullary neoplasm. The metastases, however, will show a more rapid, almost acute onset compared to the gradual, insidious onset of most primary cord tumors. The first symptom is frequently a radicular pain and/or paresthesia from the level of the metastasis. Next, there will be ipsilateral lower motor neuron weakness at the level of the metastasis and ipsilateral spastic paresis below this level. The sensory picture may be quite variable to begin with, but, in a matter of weeks, there will be a definite sensory level below the site of the metastasis, along with bilateral spastic paraparesis or quadriparesis. The comparative acuteness of onset and the rapidity of the course differentiate this picture from that of the usual primary intramedullary neoplasm.

Differentiation from an extramedullary metastasis is less certain, but, in this latter condition, the pain is more likely to be severe and tends to be localized over the involved vertebra. The clinical findings are often indistinct and bizarre until a complete obstruction occurs. With obstruction, the paraplegia, sensory level, and urinary retention are often present within a matter of hours. The lumbar puncture is frequently diagnostic in this condition.

Hematomyelia or other vascular accidents of the cord may be confused with intramedullary metastases. The discovery of a primary malignancy and the progressive course of the intramedullary metastasis will help differentiate it from vascular disease.

The diagnosis of intramedullary spinal cord metastasis has rarely been made prior to death,

mainly because the rarity of this condition excludes it from most clinicians' consideration. Of course, the keystone of the diagnosis is the discovery of the primary source. This plus the clinical picture must remain the major diagnostic points, as laboratory studies have been of little value.

Lumbar puncture, which is so often diagnostic in extradural metastases, has been of little help in cases of intramedullary metastases. The initial spinal fluid pressure was normal in all but 1 instance,[3] and the Queckenstedt maneuver has not shown clear-cut evidence of obstruction in any of the cases reported. The occurrence of clinical symptoms before the tumor becomes large enough to obstruct the spinal cord is the obvious reason for the normal spinal fluid dynamics. The cerebrospinal fluid protein level is usually at or above the upper limits of normal but does not reach the high level seen with extramedullary metastases. The cerebrospinal fluid protein ranged from 36 to 107 mg. per cent, with an average of 85 mg. per cent in the 11 procedures that have been recorded in the literature and in this report.

X-ray examination of the spine has been performed in a number of the cases but has never been of diagnostic aid. Myelograms have been performed 7 times on 5 patients, and in only 2 of these was there evidence of intramedullary enlargement. In 1 case, this was interpreted as proof of a primary spinal cord tumor,[9] and the other is Case 3 of this report. A negative myelogram is of some diagnostic value, however, for this procedure will almost invariably show the presence of extradural metastatic disease that is compromising the spinal cord.

CLINICAL COURSE AND TREATMENT

The clinical course of intramedullary spinal cord metastases has been a progressive deterioration to death within a period of a few months. In many of the cases, however, the actual cause of death has not been the spinal cord disease but other manifestations of intracranial metastasis or generalized carcinomatosis. Modern nursing technic in the care of paraplegia and quadriplegia will keep the patient with cord disease alive indefinitely, but the further course of tumor spread appears inexorable at the present time.

Treatment of this condition has been entirely unsuccessful. Surgical attack on the tumor has not been reported, and it would appear that this would be both hazardous and fruitless. High voltage roentgen therapy directed at the site of the metastasis might temporarily shrink the tumor, but x-ray to the spinal cord and nitrogen mustard therapy were tried on our 2 patients without evidence of success. Unfortunately, most of the damage is done at the time of the initial symptoms, so that any type of treatment will be of limited value.

SUMMARY

The case histories of 3 patients with pulmonary carcinoma that metastasized to the substance of the spinal cord are presented. It is felt that intramedullary cord metastases are not as rare as the few cases in the literature would indicate.

The author wishes to express his gratitude to William Hofmann, M.D., for encouragement and assistance in this study.

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Familial cerebral aneurysms including one extracranial internal carotid aneurysm

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THERE IS STILL dispute concerning the origin of aneurysms of the cerebral arteries. A clue bearing on the importance of congenital factors comes from the appearance of aneurysms in more than one member of a family. Information on this point is singularly meager. The occurrence of cerebral vascular episodes in several family members with polycystic kidneys has been known since 1904.[4] There are reports of angiomas in several members of one family.[15] Familial berry aneurysms are rare; in 1942, O'Brien[11] reported autopsy proof of a middle cerebral aneurysm in a man whose twin brother had died suddenly eight years before with the clinical impression of "either that of brain abscess ruptured into a ventricle or spontaneous hemorrhage of a congenital flaw in a brain artery." Autopsy evidence was lacking in the case of Jokl and Wolffe,[9] which also involved sudden death in identical twins. In Bruce's revision of Wilson's *Neurology*,[19] one finds "further evidence of their dysplastic origin is afforded by occasional appearance in more than one member of a family" without specific details.

Chambers, Harper, and Simpson[3] reported ruptured aneurysms in father and son, proved by angiography and operation in the father and by autopsy after 2 hemorrhages in the son (in whom angiography had failed to disclose the source of bleeding). Walton[17] has found 6 instances of familial hemorrhagic episodes (brothers, sisters, mother-and-daughter, and so on) but without specific details. Asenjo, Uiberall, and Fierro[1] refer to the case of Chambers and associates and state without elaboration, "We have a similar one." In a recent letter, Chambers told us that he has received only 1 letter, following his publication, with similar incidence of familial aneurysm. Eck[5] refers only to Chamber's article in citing proved cases of hereditary factors in cerebral aneurysms. His own experience has to do with 1 autopsied case of ruptured anterior communicating artery aneurysm with a sibling who died of a stroke in the middle 40's and with 1 pair of brothers whose autopsies showed an aneurysm of the basilar artery and 1 at the junction of the anterior cerebral and anterior communicating arteries. In the beautifully written and illustrated monograph of Krayenbühl and Yasargil,[10] mention is made of a pair of brothers with anterior communicating artery aneurysms, a father with arteriovenous malformation, and a son with an aneurysm. In view of the paucity of reports, we have thought it worthwhile to add the following case histories, which might indicate the incidence is not as low as might otherwise be suspected.

Case 1. J.G. was a right-handed, white male truck driver, aged 50, when hospitalized on the Neurosurgical Service of Dr. H. R. Oberhill at the Chicago Wesley Memorial Hospital on December 29, 1955. Eight days before admission, he had had an episode of amnesia followed by severe occipital headaches. At another hospital, spinal puncture yielded bloody cerebrospinal fluid. The headache persisted, and, five days after onset of complaints, the man became confused and incoherent, with difficulty in expression; 2 brothers were said to be in good health, the parents had died of unknown causes, and 1 brother had died following operation for bleeding intracranial aneurysm.

From the Neurosurgical Services of Chicago Wesley Memorial Hospital, St. Luke's Hospital, and the University of Illinois Research and Educational Hospitals, Chicago.

Examination revealed a confused, uncooperative, lethargic man with motor and sensory aphasia. The deep reflexes were increased in the right extremities, and the right abdominal reflexes were absent. There was bilateral papilledema. Positive Kernig's sign accompanied marked nuchal rigidity. Repeated recordings of the blood pressure ranged about 140/80 mm. Hg. Normal laboratory studies included hemogram, urinalysis, serologic test for syphilis, and x-rays of the skull and chest. Bilateral percutaneous carotid angiograms were done on December 30 and January 3, demonstrating a solitary aneurysm at the trifurcation of the left middle cerebral artery. The injections on the left were followed by a transient right hemiparesis, more in the arm than in the leg. Craniotomy on January 5 permitted clipping the base of the aneurysm, sacrificing 1 efferent arterial branch in the procedure.

Recovery was progressive, and, by the fourth postoperative week, the man was walking. There was moderate paresis of the right upper extremity, but speech was improving. Partial anomia and alexia remained when the patient was last seen in October 1956.

Case 2. J.J.G., brother of J.G. of Case 1, was hospitalized in St. Louis, in December 1952 because of head injury incurred when he lost consciousness suddenly. A ruptured aneurysm was suspected when bloody spinal fluid was obtained, but, because of a history of lues (with questionable laboratory findings), penicillin therapy was undertaken. During this treatment, a second subarachnoid hemorrhage occurred and the patient was transferred to the care of Dr. Leonard T. Furlow (to whom we are indebted for the story). At angiography on January 16, 1953, an aneurysm located on the anterior communicating artery was found. Through a right frontal craniotomy, a large frontal intracerebral hematoma was evacuated; after subtotal resection of the frontal lobe, a large saccular aneurysm was ligated. For twelve hours the patient did well, only to become stuporous. He died on the second postoperative day. Autopsy revealed impairment of hypothalamic circulation.

Comment. Papilledema with rupture of an aneurysm at the trifurcation of the middle cerebral artery is uncommon. Postangiographic hemiparesis is, alas, *not* uncommon and carries some implication of preexisting vascular impairment (either from arteriosclerosis or hypotension during the procedure or from that narrowing "spasm"), which is often found in the vicinity of an aneurysm that has leaked. The recurrence of bleeding from an aneurysm within the first two or three weeks after first rupture is the major impetus toward early diagnosis and treatment for increasing the salvage of patients with cerebral aneurysm.

Fig. 1. E.S.: left carotid angiogram (anteroposterior view) shows aneurysm at upward angulation of middle cerebral artery.

Case 3. H.A.S. was born April 23, 1909. He considered himself well until December 1, 1953, when he was suddenly dizzy, staggered, and had severe occipital headache. This persisted with stiff neck, so investigation was begun, yielding bloody spinal fluid. He was admitted to the Neuropsychiatric Institute of the University of Illinois on December 8, 1953. Aside from nuchal rigidity and bloody cerebrospinal fluid at 95 mm. pressure, examinations revealed no abnormalities. On December 10, bilateral percutaneous carotid angiography with 35% Diodrast disclosed an aneurysm of the left middle cerebral artery (Fig. 1) just before this vessel branched. On December 17, left frontotemporal osteoplastic craniotomy was done under general endotracheal anesthesia, using intravenous Arfonad to induce hypotension. The softened hemorrhagic tip of the left temporal lobe was removed with suction-cautery, disclosing the aneurysm in the anterior part of the sylvian fissure. Several large silver clips were used to occlude the aneurysm, which bled during the procedure.

Postoperatively, the man was able to move all extremities and to speak. Three days later, he was given heparin and Dicumerol because of slowed speech and general apathy. This was stopped on December 28, 1953, and the patient was discharged five days later, with slight weakness of the lower half of the right face and of the right upper extremity but without aphasia or pathologic toe or finger signs. When he was seen on May 20,

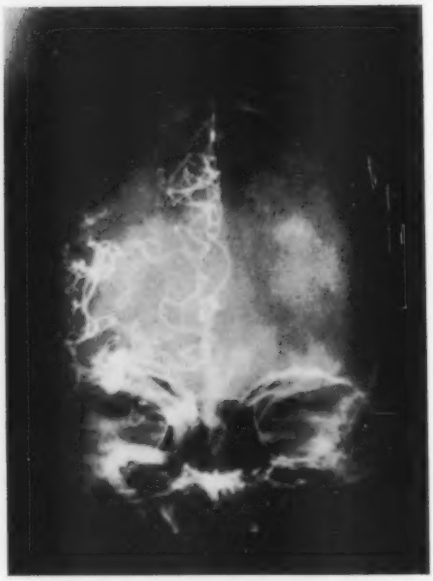

Fig. 2. H.S.: right carotid angiogram (anteroposterior view) shows aneurysm at point of division of middle cerebral artery.

1954, he had been taken off the prophylactic postoperative Dilantin therapy and was neurologically intact. Following a major seizure on January 16, 1955, he was again given anticonvulsants, which were gradually reduced to 100 mg. of Dilantin daily when he was last seen on November 8, 1956. No neurologic abnormalities were detectable three years after operation. On May 14, 1957, he was driving a car that suddenly crashed through one fence and came to rest against another. When he was extricated, he was dead. According to the autopsy report, there was a recent occlusion of the right coronary artery as well as an ancient sclerotic occlusion of the circumflex branch of the left coronary artery. Examination of the brain revealed no evidence of recent hemorrhage and no identifiable aneurysm. Several silver clips were reported to have been found in the vicinity of a superficial brownish discoloration at the junction of the frontal and temporal lobes.

Case 4. E.S., brother of H.A.S., was born March 4, 1907. He had onset of severe right-sided headache and clumsiness of the left hand on October 9, 1956. Lumbar puncture yielded yellow fluid with normal pressure, and he was discharged from the hospital on October 12. Five days later, he became restless and complained of double vision and, by October 18, had severe headache, drowsiness, and slowed speech. He was admitted on the service of Dr. Eric Oldberg at St. Luke's Hospital on October 19, 1956. The spinal fluid was dark yellow, at 260 mm. water pressure. The patient was somewhat slowed in responses and ignored objects in the left field of vision; his neck was stiff. On October 23, 1956, percutaneous carotid angiography under general anesthesia disclosed elevation of the right middle cerebral branches in the sylvian fissure, with a bulbous 5-mm. mass at the lateral extremity of the horizontal portion of the right middle cerebral artery (Fig. 2). He was transferred to the Neuropsychiatric Institute of the University of Illinois, and, on October 26, 1957, right frontotemporal craniotomy was done, with hypothermia as low as 32.2° C. (90° F.) and hypotension from Arfonad dropping the pressure from 150/110 to 80/60 mm. Hg. A large subcortical accumulation of liquid and clotted blood was evacuated from the temporal lobe. Dissection along the sylvian vessels permitted confirmation of the location of the aneurysm, which was then clipped. Postoperatively, the patient had no aggravation of his neurologic deficit, left homonymous hemianopsia. On November 6, 1956, angiography with 38% Renografin disclosed less displacement of the sylvian vessels and the aneurysm did not fill. The man was discharged on November 8, 1956, taking 100 mg. of Dilantin thrice daily. A month later, his physician wrote that he had returned to work and had no complaints.

Comment: The younger brother had his first episode of subarachnoid hemorrhage when almost 45 and died at 49 of coronary occlusion. The older brother had his first attack at 49 and is still alive. The aneurysms were in virtually identical locations on opposite sides of the head.

Case 5. On January 28, 1952, W.A., a right-handed white male herdsman, was admitted to the Chicago Memorial Hospital on the service of Dr. Paul C. Bucy. Two weeks earlier, he experienced sudden severe headache with stiffness of the neck. Lumbar puncture at that time yielded bloody cerebrospinal fluid. The patient's brother died of "cerebral hemorrhage" at 45, and the son of the brother had died of "cerebral hemorrhage" at 28. Examination revealed systemic blood pressure of 118/80 mm. Hg. Partial deafness on the right and hyperactivity of the right knee jerk were the only peculiarities in the neurologic examination. Laboratory studies of blood and urine were normal. Left carotid angiography on January 30, 1952, showed an aneurysm arising "from the internal carotid artery" at the supraclinoid level. The left common carotid artery was ligated in the neck on February 5, 1952, and recovery was uneventful. The patient continued to have minor headaches precipitated by ingestion of alcoholic drinks. He returned to full activity until, on December 9, 1955, he

became suddenly week and "dizzy" and could not stand. He was unconscious for about fifteen minutes and had urinary incontinence. On awakening, he was able to rise to his feet but noticed weakness of the right extremities. About an hour later, severe generalized headaches and stiff neck began; several hours later, the right extremities regained their strength. Aside from meningism, no new abnormalities were found on neurologic examination. Grossly bloody cerebrospinal fluid was present under increased pressure when puncture was done on December 13, 1955. Bilateral percutaneous angiography of the carotid vessels was done on this day and two days later, revealing 4 aneurysms (Figs. 3 and 4); 2 were at the trifurcations of the right and left middle cerebral arteries, 1 was on the anterior communicating artery, and the fourth was an extracranial aneurysm on the left internal carotid artery at the level of the angle of the mandible. Review of the angiograms from 1952 disclosed the same aneurysm outside the head, which had been overlooked earlier. The patient was put at complete bed rest but died suddenly on December 27, 1955. Autopsy revealed massive bilateral frontal intracerebral hematomas and subarachnoid hemorrhage, apparently from rupture of the aneurysm of the anterior communicating artery. There was no evidence of prior bleeding from any of the other aneurysms, which were found in positions predicted from the angiograms.

No postmortem examination was done in the case of the brother who had died at 45, but a brief account of his son's illness follows.

Case 6. R.H.A., nephew of W.A., complained of headaches for years and on 3 occasions was hospitalized for "anxiety tension state." On the morning of March 21, 1945, at age 28, he complained of weakness and later had profuse diaphoresis and vomiting. He was placed in an Army Air Force Hospital, given sedation, and put at bed rest. He died three hours later. Autopsy was done, and, according to the Armed Forces Institute of Pathology, there was a ruptured saccular aneurysm involving the junction of the left anterior cerebral and anterior communicating arteries. Hemorrhage had extended into both frontal lobes and into the cerebral ventricles. No other systemic anomalies were found.

Comment. In the case of W.A., complete angiography done originally might have helped to decide proper treatment, but it is not clear whether cervical ligation helped this man or made matters worse, for the site of the first bleeding is not known. It seems likely that the anterior communicating artery aneurysm ruptured, and common carotid artery ligation would not be expected to help such a situation. Perhaps it did not—the improvement may

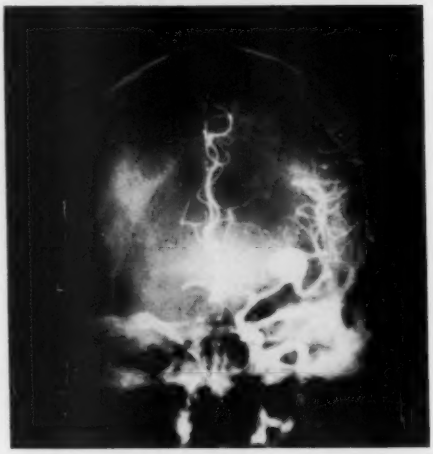

Fig. 3. W.A.: left carotid angiogram (anteroposterior view) with aneurysms of anterior communicating and left middle cerebral vessels

Fig. 4. W.A.: right carotid angiogram (lateral view) with extracranial and intracranial aneurysms

Fig. 5. J.G.: left carotid angiogram (lateral view) with aneurysm at bifurcation of internal carotid artery

have been in spite of the ligation, not because of it. The treatment of subarachnoid hemorrhage in the presence of multiple aneurysms is not easy, for the location of the rupture is usually not clear. We have looked for evidence of vascular displacement due to hematoma and narrowed vessels "in spasm" in the neighborhood of the ruptured vessel. Such localizing signs are usually absent or, if present, may be deceptive. Intracerebral hematoma is not too common with a first bleeding and recovery. Atresia or stenosis of components of the circle of Willis is common, and what appears to be spasm from nearby hemorrhage may, in fact, be normal for a given patient.

Neither of us have encountered nontraumatic aneurysms on the extracranial portion of the internal carotid artery before. Literature survey shows they exist. Rydell and Jennings[13] have reviewed the surgical treatment of cervical carotid aneurysms and added to the relatively few cases reported 2 of their own (man, 67, with acute arteritis and aneurysm; woman, 74, with aneurysm of unknown origin but of two years' duration). Krayenbühl and Yasargil[10] refer to 3 extracranial carotid aneurysms among the 276 saccular aneurysms they have encountered; 1 is referred to by Hardy and associates[7] and Dr. Gurdjian wrote concerning it: "A portion of it presented in the form of a mass in the mouth in the region of the tonsil. Because of the pulsations before a proposed tonsillectomy, Dr. Bruce Proctor was clever enough to put a needle in the pulsating mass. To his surprise there was severe bleeding. The patient was then referred to our service and an angiogram was performed which showed the mass in the neck. It was fairly simple to excise it."

Multiple aneurysms within the head are well known. Williams, Bahn, and Sayre[18] report 1 patient with 5, 1 with 4, and 22 with 2 aneurysms each in their series of 172 aneurysms in 143 patients. Paillas and associates[12] found 6 instances of multiple aneurysm in 44 cases, while Housepian and Pool[8] found 14 cases of multiple aneurysm in 113 cases with aneurysm from the autopsy files at the Presbyterian Hospital over a forty-one-year period. Up to 5 aneurysms were found in a single case. Earlier reports can be found summarized in Bigelow's[2] article.

Case 7. J.G., 32, had severe headache on October 15, 1954, preceded by sharp shooting pains behind the left eye for two days. He had headache, lethargy, and stiff neck. A week later, lumbar puncture revealed bloody spinal fluid. On October 26, he had a major seizure and his lethargy increased. He was admitted to the St. Luke's Hospital on the service of Dr. Eric Oldberg on October 28, 1954—lethargic but oriented. No stretch reflexes were elicitable in the arms, but they were present in the legs. There was a positive Chaddock's sign on the left, and a questionably positive one on the right. The neck was stiff. Two days later, Babinski signs were equivocal but Chaddock's sign was present on each side. Spinal puncture yielded uniformly pink fluid, with 100% crenated red blood cells, under 320 mm. fluid pressure. On November 1, 1954, percutaneous carotid angiography revealed an aneurysm at the bifurcation of the left internal carotid artery (Fig. 5). On the afternoon of November 4, 1954, the left common carotid artery was ligated under local anesthesia. Fifteen hours later, the man became hemiparetic and aphasic. With inhalations of 5% carbon dioxide in oxygen and injections of papaverine (0.1 gm. every six hours), his condition gradually improved. By November 11, he was using his right arm well and speaking fluently. When last seen on February 4, 1955, his only residue was a slight right facial weakness and subjective hesitancy when using unusual words. A

letter from his doctor on September 27, 1957, mentions mild aphasia responsible for a lack of desire to be around other people.

Case 8. R.S., sister of J.G., was 40 when admitted to Mt. Sinai Hospital in Chicago on the service of Dr. Ben Lichtenstein, to whom we are indebted for this case presentation. She had had headaches of short duration throughout her life, and they became prominent in the fall of 1956 and severe in March 1957. In mid-March, she complained of severe pain behind the right eye and in the right temple. On March 24, 1957, she had a major convulsion. Examination on hospitalization on the following day showed the blood pressure to be 112/70 mm. Hg; there was a left Babinski sign and increased left patellar reflex, and the neck was stiff. Lumbar puncture yielded bloody fluid under 150 mm. water pressure. On March 27, 1957, Dr. Paul Rosenbluth carried out carotid angiography that disclosed an aneurysm of the right internal carotid artery just above the siphon (Fig. 6). A Selverstone clamp was put on the common carotid artery, tightened about 50% the first day, and then gradually closed over the next two days. The external stem was removed on April 1, 1957. On March 30, retinal artery pressures were 30 mm. on the right and 80 mm. on the left. Vision remained good. On April 3, 1957, confusion led to lumbar puncture, which showed yellow fluid at 220 mm. pressure. Urinary incontinence persisted until April 12, by which time her neck was supple. She was discharged, improved, on April 15, 1957.

Comment. At the time of the operation on J.G., heparin was injected into the distal portions of the carotid artery to minimize postoperative thrombosis, and the patient was given Dicumerol during the prior twenty-four hours. (It was then the practice of Dr. Sugar to give anticoagulants routinely, in accordance with suggestions of Dr. James Poppen.) When he developed aphasia, stellate blocks were not done lest mediastinal hemorrhage occur, even with the relatively innocuous anterior approach. It has been our experience that the postoperative difficulties are rarely those of thrombosis and much more commonly are those of ischemia, so the use of anticoagulants has been stopped. With the present use of Salibi's modification of Selverstone's clamp, which can be readily released, complications from ischemia have been rare (although they still occur).

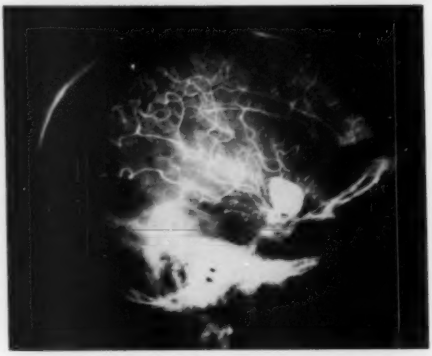

Fig. 6. M.S.: right carotid angiogram (lateral view) with aneurysm of internal carotid near its bifurcation

DISCUSSION

Arteriosclerotic lesions of the large vessels of the brain are common and have preferential loci, as Fisher[6] has pointed out. The incidence of aneurysms in these arteriosclerotic patients is low, and it seems to us that the basic lesion must be congenital. Whether some arteriosclerotic lesion must be superimposed, as Walker and Allegre[16] have proposed, is a moot question. In a recent patient who died of ruptured carotid aneurysm after carotid angiography on both sides had failed to disclose an aneurysm, the presumably normal second side also had an aneurysm and histologic study of this small unruptured aneurysm showed no sign of atherosclerosis other than deficiency of the elastic layer in the wall of the aneurysm. Nowhere else in the entire circle of Willis could any gross evidence of arteriosclerosis be found. The present series of cases of aneurysm in several members of a family, sometimes with similar loci, would support the concept of the congenital origin of so-called berry aneurysms.[14] We hope that others will be encouraged to look for and report their cases of familial aneurysms.

SUMMARY AND CONCLUSIONS

1] A total of 4 pairs of cases of aneurysms in members of the same family are reported (2 pairs of brothers, 1 uncle-nephew pair, and 1 brother-sister pair).

2] Of these, 1 patient had 4 aneurysms, 1 of which was on the extracranial portion of the internal carotid artery at the level of the angle of the mandible.

3] These instances are taken to support the concept of the primary congenital origin of cerebral aneurysms.

ADDENDUM

After completion of this article, the authors were informed of another case report concerning familial aneurysms. Ross[20] saw a 32-year-old woman with left parietooccipital angioma in the right temporal fossa and aneurysm of the left middle cerebral artery. Her mother, 64, had a clamp put on a carotid artery for aneurysm with subarachnoid hemorrhage but died at home of a second subarachnoid hemorrhage nine days after discharge from hospital.

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Familial progressive bulbar-spinal muscular atrophy

Kenneth R. Magee, M.D.

THIS PAPER presents a family with clinically and pathologically documented progressive muscular atrophy beginning in adult life, chronic in duration, with both spinal and bulbar manifestations. All affected members were examined by the author. In addition, the diagnosis was confirmed by electromyography, muscle biopsy and, in 1 case, necropsy. During the past century, there has been much discussion and confusion regarding the appropriate classification of degenerative motor neuron disease. Therefore, prior to a review of the genetic aspects of progressive muscular atrophy and presentation of the cases, it is important to define my use of the term "progressive muscular atrophy."

A problem in classification can be anticipated in view of the lack of knowledge regarding the etiology (or etiologies) of this disorder. The literature contains many reports in which progressive spinal muscular atrophy, chronic poliomyelitis, and amyotrophic lateral sclerosis are regarded as the same disease. Other authors differentiate these disorders as well as their longitudinal variant, progressive bulbar palsy. Also adding to the confusion of definition is the occasional use of the term progressive muscular atrophy for Charcot-Marie-Tooth disease, although more commonly the latter disorder is called progressive neural or peroneal muscular atrophy.

Adams, Denny-Brown, and Pearson,[1] Merritt,[2] Brain,[3] and Nielsen[4] believe that progressive muscular atrophy is but a variant of amyotrophic lateral sclerosis, in which the lesions are limited to lower motor neuron. It is emphasized that many patients showing clinical lesions limited to the lower motor neuron often show evidence of corticospinal tract degeneration on postmortem examination.

On the other hand, Alpers,[5] Wechsler,[6] and Müller[7] feel that, at present, it is better to consider progressive muscular atrophy, with lesions limited to the lower motor neuron, a separate clinical entity, particularly because of the better prognosis. This view is also expressed by Kinnier Wilson,[8] who states, "Difficult as it is to reach a firm conclusion, the lesions of the Charcot type are so characteristic, and, when advanced, so different from those of nuclear amyotrophy, that in my opinion the fact outweighs other considerations; they comprise much more than the mere addition of upper to lower motor neuronic disease."

Müller[7] considered prognosis in detail by reviewing 190 cases of progressive motor neuron disease in adults in Sweden. In this group, he again confirmed that amyotrophic lateral sclerosis, especially when associated with bulbar palsy, was a relatively rapidly fatal disorder; 78% of patients in his series who did not have bulbar palsy and 92% of those who did, died within three years. On the other hand, 7 patients who clinically had lower motor neuron disease without upper motor neuron lesions or bulbar palsy were alive eight to thirty years after the onset of their disability. From his clinical data, he concluded that a pure progressive spinal muscular atrophy exists, constituting a different morbid state. He commented that even pathologic involvement of the corticospinal tract does not prove that the case is one of amyotrophic lateral sclerosis, for the same structures in the central nervous

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This study was assisted by a grant from the Michigan Alumni Fund–Faculty Research Equipment Fund of the Horace H. Rackham School of Graduate Studies of the University of Michigan.

system may conceivably be involved in different morbid states.

Thus, briefly summarizing the extensive literature, certain obvious points regarding degenerative motor neuron disease emerge, regardless of any attempt to draw conclusions regarding etiology. [1] There are several definite clinically and pathologically documented types of progressive motor neuron disease—the Werdnig-Hoffmann type of infantile progressive muscular atrophy, the Charcot-Marie-Tooth form of progressive (neural) muscular atrophy, and the relatively rapidly fatal amyotrophic lateral sclerosis of Charcot, presenting with both upper and lower motor neuron symptoms. [2] There are certain cases of amyotrophic lateral sclerosis seen at an early stage with signs of only lower motor neuron disease that eventually will develop clinical evidence of upper motor neuron involvement. [3] Certain cases of amyotrophic lateral sclerosis may have such profound lower motor neuron involvement that clinical signs of corticospinal tract damage are masked. [4] In some patients who demonstrate only lower motor neuron involvement throughout the course of the disease, evidence of corticospinal tract damage may often be found on postmortem examination. This presumably correlates with the previous point. [5] Progressive bulbar palsy is merely a variant of motor neuron disease, and, regardless of the arguments concerning the identity of amyotrophic lateral sclerosis and progressive spinal muscular atrophy, bulbar palsy may occur as a manifestation of either type and usually indicates a poorer prognosis than when the disease begins in the peripheral musculature. [6] It is reported again and again throughout the literature that patients who have only lower motor neuron disease often have a more benign prognosis than those with both upper and lower motor neuron disease. [7] So-called primary lateral sclerosis may occur as an isolated entity, but many patients eventually show the syndrome of amyotrophic lateral sclerosis in the same manner that patients manifesting only lower motor neuron involvement initially may eventually have corticospinal tract signs. However, other disorders (multiple sclerosis, cord tumors, or syphilis) may be confused with primary lateral sclerosis, and this renders its exact diagnosis and evaluation in a study of degenerative motor neuron disease very difficult. [8] So-called progressive nuclear ophthalmoplegia has often been regarded as an additional variant of motor neuron disease, but its association with amyotrophic lateral sclerosis, progressive muscular atrophy, or progressive bulbar palsy is not common; it is not a clear-cut pathologic entity, nor has it even been proven to be related to these other disorders. Many authors feel that it is much more likely to be a dystrophy of the extraocular muscles.

With these observations in mind, it seems that progressive muscular atrophy, manifesting only lower motor neuron signs (of either spinal or bulbar involvement), should be considered, primarily because of its slower course, a clinical entity separate from amyotrophic lateral sclerosis until further information regarding etiology of these disorders is available. The profound prognostic importance renders such distinction of far more than academic interest, although it certainly must be admitted that these types of degenerative motor neuron disease may be proved eventually to have a similar etiology and merely be variants on a spectrum ranging from primary lateral sclerosis on one side to progressive muscular atrophy on the other.

For prognostic reasons, the differential diagnosis must be made with care and, indeed, often cannot be made with assurance in early stages. The following criteria, obviously at times impossible to ascertain, are necessary to establish the diagnosis of progressive muscular atrophy as used henceforth in this paper: [1] Patients must be excluded when anterior horn cell damage is so early or severe that clinical signs of corticospinal tract damage have not appeared or are masked. Such determination is, of course, often difficult or impossible even for the experienced neurologist. [2] Similarly, patients must be excluded who are observed at an advanced stage when lower motor neuron disease is so severe that corticospinal tract signs, once present, have disappeared. If this differentiation is not made, in a sense all patients with amyotrophic lateral sclerosis may potentially show a picture of only progressive muscular atrophy. This is fairly simple to

determine in contrast to the previous point, for by this time the neurologist definitely knows the rate of progression of the disease in the patient and information from earlier examinations is often available. [3] With the exceptions noted above, to make a diagnosis of true progressive spinal (and bulbar) muscular atrophy, a patient must show only the classical atrophic hyporeflexic flaccid lower motor neuron type of paralysis, usually with fasciculations. Upper motor neuron signs must be absent. In this respect, it must be remembered that even normal or "brisk" reflexes in a patient with degenerative lower motor neuron disease may be suggestive if not positive evidence of corticospinal tract involvement.

GENETIC CONSIDERATIONS

Because of changing concepts and classifications of degenerative motor neuron disease, it is most difficult to evaluate the hereditary aspects of these disorders. If, at least for the purpose of this report, it is accepted that progressive spinal muscular atrophy and amyotrophic lateral sclerosis are separate clinical entities, a review of the literature discloses no fully documented cases of familial progressive muscular atrophy. The majority of patients described as having progressive muscular atrophy seem much more likely to have had amyotrophic lateral sclerosis when the physical findings and course of the disease are studied. Hereditary amyotrophic lateral sclerosis is also very rare, except for the disease reported by Koerner,[9] Arnold, Edgren, and Palladino,[10] Kurland and Mulder,[11] and others on Guam and adjacent islands, which is clinically indistinguishable from amyotrophic lateral sclerosis as seen in this country. Kurland and Mulder,[12] however, reviewed hereditary cases of amyotrophic lateral sclerosis and found that, from 1850 to 1955, there were at least 18 pedigrees involving 90 individuals. They added 6 pedigrees with 34 individuals and concluded that amyotrophic lateral sclerosis does occur on a hereditary basis and may well constitute a significant proportion of all cases. Kurland and Mulder included progressive muscular atrophy and progressive bulbar palsy under amyotrophic lateral sclerosis. However, in the majority of their patients, the duration of illness was only about two years, the longest being three and one-half years. Their review of the literature disclosed the longest duration to be seven years in the Wetherbee (Massachusetts) family.

Because of the study of Kurland and Mulder, it is unnecessary to review the general genetic aspects of degenerative motor neuron disease. However, certain papers concerning the inheritance of so-called progressive spinal muscular atrophy must be mentioned. Clear-cut amyotrophic lateral sclerosis need not be considered nor will the well-defined entities, the Werdnig-Hoffmann form of infantile progressive spinal muscular atrophy or the Charcot-Marie-Tooth form of progressive neural muscular atrophy.

Many patients reported as having familial progressive muscular atrophy cannot be classified into any known disorder, either due to insufficient clinical information or lack of pathologic verification. This is particularly true of the early cases. A rapidly progressive muscular atrophy was described by Eichorst[13] (1873); 13 individuals in 6 generations were affected with ages of onset varying from 8 to 26. The age of onset and rapid course remove this from the category of progressive muscular atrophy as considered in this paper.

Early reports of degenerative motor neuron disease occasionally included in discussions of progressive spinal muscular atrophy are those of Holmes[14] (1905), Gee[15] (1889), Ormerad[16] (1904), and Maas[17] (1904). A familial tendency was present in all, but the onset of the disease was in early childhood, generally beginning with spastic paralysis of the lower extremities, with subsequent wasting in the hands and general amyotrophy. Kinnier Wilson[8] comments that some of these familial amyotrophic or bulbar forms show "features so alien to the generic picture as to perhaps be wrongly included in the class." Robertson[18] noted this and in fairness points out that these early authors did not try to classify their patients with any usual type of degenerative motor neuron disease. For example, Holmes reported "family spastic paralysis associated with amyotrophy."

As Robertson observed, numerous rather atypical cases of familial incidence of motor

neuron disease have been noted in youthful patients and reported cases of direct inheritance are rare, but in the latter the disease process is more typical and the patients older. He agreed with Gowers,[19] who stated that direct inheritance seems to be most common in cases that occur late in life and that, when many members of a family suffer from muscular atrophy, the disease is nearly always myopathic and not spinal in origin.

At the American Neurological Association Meeting in 1931, Moleen, Johnson, and Dixon[20] reported 3 brothers with "familial progressive muscular atrophy." However, doubt must be thrown upon the diagnosis for the following reasons, all of which suggest that the brothers are examples of myotonic dystrophy: [1] the photograph of the brothers shows baldness in at least 2 and the typical "swan neck" appearance in all 3; [2] the illustrations of muscle pathology show many internal nuclei in larger fibers, suggesting a dystrophic process; [3] atrophy of the testis was noted at autopsy in 1 brother; [4] despite the severe wasting of skeletal muscles, necropsy findings showed reduction in the anterior horn cells of the upper 4 lumbar segments by only 30% and, in the cervical and thoracic segments, the anterior horn cells were normal; [5] it is stated in the text that the "predominance of strength in the flexors was further evident in the grasping of objects; the patient found difficulty in relaxing the grasp, the extensors being too weak to overcome the contraction of the flexors which, on fixation in a hyperextended position, became markedly contracted." Also, "he had a subjective sensation of cramping with the inauguration of a movement," and "tapping the right forearm extensor tendon caused a slight extension of the fingers, which slowly relaxed." All of these quotations are compatible with myotonia.

Early reports of progressive muscular atrophy, chronic poliomyelitis, or "progressive spinal myopathy" include those of Osler,[21] Dana,[22] Robinson,[23] Lovell,[24] and Hamilton.[25] In all these reports, more than 1 generation was affected. The relatively rapid course with death occurring within a few years suggests amyotrophic lateral sclerosis. An autopsy on Hamilton's case showed pyramidal tract and anterior horn cell abnormalities. Robertson[18] also reported familial progressive bulbar palsy occurring in 2 males and 2 females in 2 generations. An unusual aspect of this case was intellectual impairment. After death a little over a year after onset of symptoms, postmortem examination disclosed loss and atrophy of the large pyramidal cells of the motor cortex but no demyelination of any column. Atrophy of nerve cells in the hypoglossal nucleus, the dorsal motor nucleus of the vagus, and the motor nerve cells in the anterior horns of the cervical and upper dorsal regions of the cord was present.

Myrianthopoulos and Brown[26] presented 2 families as examples of hereditary progressive muscular atrophy. In both families, varying degrees of ptosis was the most common manifestation, the condition often appearing without other neurologic findings. There does not seem to be sufficient evidence to rule out a primary myopathy.

The only reference in the literature to a family possibly similar to the one to be reported was mentioned by Kurland[27] in a brief addendum to a review of genetic aspects of amyotrophic lateral sclerosis. He mentions a Japanese family in which 2 brothers were affected by a slow progressive lower motor neuron disease of twenty years' duration, which was also present in 3 other males in the preceding 2 generations. He mentions another Japanese male of 45 with similar weakness of bulbar and cervical musculature with slow progression over a seven-year period, who had a brother who was said to be affected by a slowly progressive bulbar palsy. Unfortunately, these patients are not described in sufficient detail for full documentation.

Additional hereditary examples of relatively clear-cut amyotrophic lateral sclerosis have been reviewed with pedigrees by Kurland and Mulder. In these reports, more than 1 generation was affected. They comment that the pedigrees are compatible with dominant inheritance and that, although recessive inheritance must be considered, the extremely low probability of observing this disorder in successive generations so consistently makes this form of inheritance unlikely.

Thus, this review suggests: [1] there has

been no fully documented example of a pure progressive spinal and bulbar muscular atrophy of chronic duration showing inheritance of any type. [2] Whether considering amyotrophic lateral sclerosis, progressive muscular atrophy, or progressive bulbar palsy, the fully documented reports in the literature have not suggested recessive inheritance.

RESUME OF CLINICAL AND GENETIC FEATURES

Beginning at ages 52, 50, and 40, 3 brothers of English descent developed progressive weakness that began in the distal extremities in 2 and in the bulbar musculature in the third. The weakness became generalized and involved both spinal and bulbar musculature. The rate of progression was very slow.

The clinical findings were similar in all, although the severity of involvement varied. The weakness was generalized and included both spinal and bulbar muscles, with the distal extremity musculature slightly weaker than the proximal. Varying degrees of atrophy were present. Deep tendon reflexes were absent. Fasciculations were striking and were observed in extremities, trunk, neck, face, and tongue. Tone was either normal or reduced. No signs of corticospinal tract involvement were present. Of interest, considering the general involvement of somatic efferent muscles, was the complete sparing of the extraocular muscles in all patients.

Laboratory studies disclosed normal blood count, urinalysis, fasting glucose, and serology in all. Thyroid function was normal. Spinal fluid examination was normal except for a slight elevation in protein in 1 patient. Electromyograms disclosed numerous fasciculations and fibrillations in each patient. Muscle biopsies suggested neurogenic atrophy of muscle. In the fifteenth year of his illness, 1 brother died and postmortem examination was performed.

The pedigree of the family is presented in Figure 1. The most probable method of transmission can be seen to be recessive. It is not, however, possible to ascertain with assurance whether it is an autosomal or sex-linked recessive.

The 61-year-old unaffected brother was not examined. However, his job consisted of heavy labor and truck driving, and it would seem that he possessed greater than normal strength

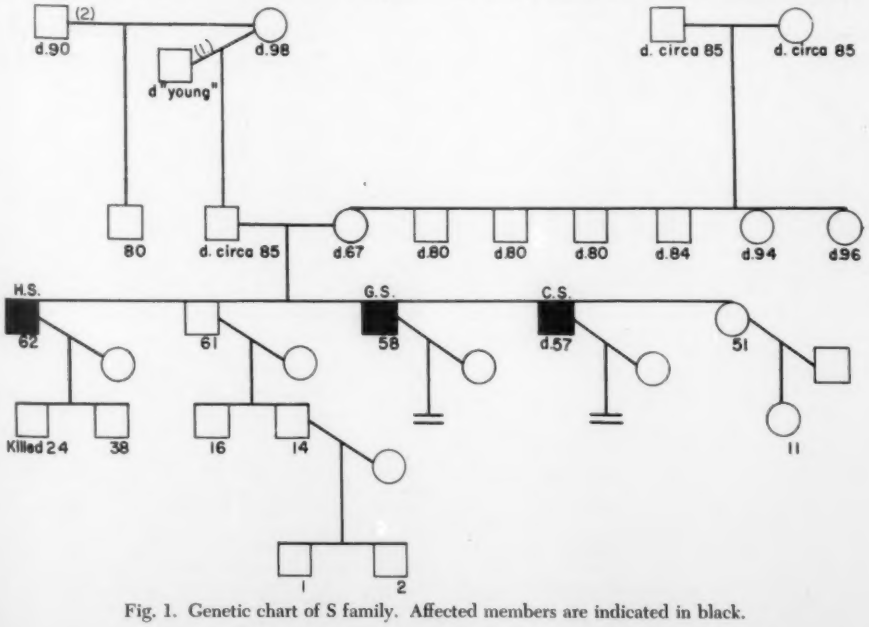

Fig. 1. Genetic chart of S family. Affected members are indicated in black.

Fig. 2. (*Case 1*) Although slight atrophy is evident in the shoulder girdle, this photograph, taken in the seventh year of the patient's illness, illustrates how slowly the man's disorder has progressed.

throughout life and, at least, certainly was not weak.

The 50-year-old sister of the affected brothers was seen and examined by the author. There was no history to suggest any type of neurologic disease. Complete neurologic examination was within normal limits.

As the pedigree indicates, most other members of the family lived to advanced ages and none had motor disorders.

CASE REPORTS

Case 1. H. S., a 60-year-old white male, noted the onset and slow progression of fatigue and weakness when chewing and a mild dysphagia for solids in 1950 at the age of 52. One year later, he had weakness of the left hand, which, during the next six months, spread to shoulder, and a similar, but very mild, weakness also appeared in the right upper extremity. Around six months later, he noticed weakness in the left lower extremity, beginning distally but within six months spreading to the proximal muscles, with consequent difficulty in climbing and rapid walking. The course of his illness then remained relatively stationary for about three years, after which, however, the right side became similarly involved with weakness beginning in the distal and spreading to the proximal muscles in the lower extremity. The previous mild paresis of the right upper extemity became more severe. Throughout the course of the illness the patient developed atrophy and felt fasciculations in the areas where weakness developed. In the sixth year of his illness, the patient noted weakness and wasting of the facial muscles. His voice became weak, but he did not complain of difficulty in breathing. Despite the spread of the weakness and atrophy to involve all peripheral and bulbar musculature, the rate of progression was extremely slow. At no time did the patient have sensory complaints or sphincter disturbances.

The past medical history disclosed good health to the time of the present illness.

Examination. (February 1957) General physical examination was normal. Mental status was normal. Examination of cranial nerve functions disclosed slight weakness of the muscles of mastication and of the facial and pharyngeal muscles. His voice was weak and nasal. The palatal reflex was slightly reduced. The jaw jerk was not present. Atrophy and fasciculations of the tongue were evident. Fasciculations of the lower facial muscles were observed. The sternomastoid and trapezius were weak. Examination of trunk and extremity musculature disclosed diffuse symmetric weakness, most pronounced distally, in both upper and lower extremities. Only adduction of the shoulders and thigh were considered normal. Despite the weakness, all muscles could act against gravity and some resistance. There was slight generalized muscular atrophy, most noticeable in the intrinsic hand muscles and the shoulder girdle (Fig. 2). Fasciculations were observed throughout the shoulder girdles, arms, forearms, thighs, and calves. The patient's gait was waddling, and, to rise from a sitting position, he had to push himself up with his hands. The deep tendon reflexes were absent. Abdominal reflexes were present. There were no pathologic pyramidal reflexes, myotonia, or other abnormalities of muscle tone. Sensation as well as the remainder of the neurologic examination was normal.

Laboratory examinations. Chest roentgenogram, blood count, and urinalysis were normal. Blood studies disclosed serology, negative and fasting glucose, 82, calcium, 9.6, inorganic phosphorus, 3.6, and creatinine, 4.2 per 100 cc.; with protein bound iodine, 4.3 and inorganic iodine, 2μg. per 100 cc. A lumbar puncture showed clear fluid under normal pressure with no increase in cells. Chemical studies disclosed serology, negative; total protein 40 mg. per 100 cc.; colloidal gold, 0000000000; mastic, 000000; and globulin, negative. Electrocardiogram disclosed sinus tachycardia but was otherwise normal. Urinary amino acid excretion was normal. An electromyogram disclosed evidence of diffuse lower motor neuron disease with fibrillations and fasciculations in all extremities. Biopsy of the vastus lateralis showed characteristic changes of neurogenic atrophy with groups of small atrophic fibers. Moderate increase in connective tissue and fat was present.

Course. The patient has been followed to the present. He does not feel that there has been any further progression in the degree of weakness since his hospitalization. Examinations at three-month intervals have confirmed his observations.

Case 2. G. S., a 59-year-old white male, noticed slight weakness in both upper and lower extremities in 1949 at the age of 50. The weakness was initially distal and much worse in the lower than

upper extremities, but over the next year it spread proximally. He developed difficulty in climbing stairs and had to change to a job involving little walking. The weakness in the upper extremities remained minimal until the second year of the illness, when it increased considerably. The left upper extremity was slightly weaker than the right. Wherever weakness was noted by the patient, some degree of atrophy developed and fasciculations were observed and felt.

The patient was seen in 1950 for the first time at the University of Michigan Medical Center. General physical examination was normal. Mental status was normal. Examination of cranial nerve function disclosed a high pitched voice, some generalized facial weakness, and an atrophic tongue showing many fasciculations. His gait was slightly unsteady, and he had definite difficulty in rising from a chair without pushing himself up with his hands. Generalized weakness was present, most pronounced in the hands and wrist in the upper extremities and in the extensors of the hips in the lower extremities. Atrophy was slight about the shoulder girdle and definite in the small muscles of the hand bilaterally. Fasciculations were present throughout the shoulder girdle, upper extremities, abdominal muscles, anterior and posterior thigh muscles, and posterior calf muscles. Tone was normal. Deep tendon reflexes were diminished in the upper extremities, and the patellar and Achilles reflexes were absent. Abdominal reflexes were obtained but were weak. Pathologic pyramidal signs were absent. Sensation as well as the remainder of the neurologic examination was normal. At that time, a diagnosis of progressive spinal and bulbar muscular atrophy was made.

In subsequent years, the patient's weakness very slowly increased. Difficulty in climbing stairs and raising the arms above the shoulders became severe. Despite the positive findings on the earlier cranial nerve examination, the patient did not complain of chewing or swallowing difficulty until 1955, when his voice also became weak and nasal. The bulbar symptoms progressed slowly but were not severe. Shortly before his second admission to the hospital, the patient reported that his right leg and left arm were weakest but no skeletal muscle was of normal strength. Further progression of atrophy was noted, and this now seemed to precede weakness by a few months. Throughout the course of the illness, the patient did not complain of sensory or sphincter disturbances.

Examination. (February, 1957) General physical examination was normal. Mental status was intact. With the exception of the extraocular muscles, all muscles supplied by cranial nerves were slightly weak. The tongue was atrophic. Fasciculations were present in the face and tongue. The patient's voice was weak and nasal. The palatal reflex was diminished. The jaw jerk was not obtained. Motor examination of trunk and extremities disclosed slight generalized muscular atrophy (Fig. 3). Fasciculations were observed in nearly all muscle groups in the upper and lower extremities and on the trunk. There was diffuse generalized weakness, slightly more pronounced distally and slightly greater in the left lower extremity. The only muscle groups that were near normal strength were the adductors of the shoulders and adductors of the thighs. Tone was normal. The deep tendon reflexes were absent. There were no pathologic pyramidal reflexes or myotonia. Sensation, as well as the remainder of the neurologic examination, was normal.

Laboratory examinations. Chest roentgenogram, blood count, and urinalysis were normal. Blood studies disclosed protein bound iodine, 7.3 μg. per 100 cc.; potassium, 4.6 mEq. per liter; and calcium, 9.4, inorganic phosphorus, 3.5, and fasting glucose, 79 mg. per 100 cc. A lumbar puncture showed clear fluid under normal pressure with no increase in cells. Chemical studies disclosed sugar, normal; total protein, 34 mg. per 100 cc.; colloidal gold, 0000000000; mastic, 000000; globulin, negative; and serology, negative. Urinary amino acids showed a mild amino aciduria, suggested particularly by an increase in valine excretion. Electromyography showed numerous fasciculations and fibrillations in all 4 extremities. Biopsy of the vastus lateralis showed characteristic groups of small atrophic fibers, suggesting neurogenic atrophy of muscles. A moderate increase of fat and connective tissue was present.

Fig. 3. *(Case 2)* Although the atrophy was mild, this and the preceding photograph do not fully indicate its extent.

Course. The patient has been followed to the present time with only very slight progression of weakness. During this time, the left lower extremity has become proportionately weaker than other muscle groups. The total duration to date of the disease has therefore been about ten years.

Case 3. C. S., a 54-year-old white male, first noted weakness in his lower extremities in 1942 at the age of 40. The weakness seemed to de-

Figure 4

Figure 5

Fig. 4. (*Case 3*) Note the generalized atrophy. Fig. 5. Profile of same patient.

velop in both distal and proximal musculature at the same time. The patient primarily complained of difficulty in rising from a sitting position and in walking rapidly. The lower extremity weakness very slowly progressed, and, after about ten years, he also had weakness of the muscles of the upper extremities, beginning distally but within a year involving proximal musculature as well. After another 4 years (in 1956), the muscles of his neck and face became weak and he complained of difficulty in chewing, swallowing, and speaking. Throughout the entire course of the illness, muscle wasting and fasciculations developed along with the weakness. There were no sensory complaints or sphincter disturbances.

The patient's health prior to the onset of this illness was good. However, in 1951, nine years after the onset of the present illness, a mediastinal tumor was found on chest roentgenogram taken during hospitalization elsewhere because of frequent respiratory infections. A thymoma was surgically removed. Subsequent to the operation, it was thought that the patient might have myasthenia gravis and neostigmine was given, resulting in a very slight increase in strength. Neostigmine was given intermittently throughout the years, but the patient did not feel that it was particularly beneficial.

Examination. (February, 1957) General physical examination disclosed marked emaciation. A well-healed sternal scar was noted. The remainder of the general physical examination was normal. Mental status was normal. Examination of cranial nerve function disclosed weakness, atrophy, and fasciculations in the jaw muscles, facial musculature, and tongue. The jaw jerk could not be obtained. The palatal movements were reduced and the palatal reflex depressed. His voice was weak and nasal. The sternomastoid and trapezius were weak bilaterally. The extraocular muscles and sensory components of the cranial nerves were normal. Motor examination of the trunk and extremities disclosed profound generalized weakness and atrophy (Figs. 4 and 5). The weakness was more pronounced distally, although the difference from the proximal muscles was minimal. Fasciculations were present throughout the trunk and extremities. The deep tendon, abdominal, and cremasteric reflexes were absent. There were no pathologic pyramidal reflexes, spasticity, or myotonia. Sensory examination as well as the remainder of the neurologic examination was normal.

Laboratory examinations. Blood count and urinalysis were normal. Blood studies disclosed fasting glucose, 78, nonprotein nitrogen, 30, and total bilirubin, 0.4 mg. per 100 cc.; total protein, 8 gm. per 100 cc. with 4.6 gm. albumin and 3.4 gm. globulin; protein bound iodine, 5.8 μg. per 100 cc. with 2 μg. per 100 cc. inorganic iodine; creatinine, 0.42 mg. per 100 cc.; and serology, negative. A lumbar puncture showed clear fluid under normal pressure. Chemical studies disclosed total protein, 53 mg. per 100 cc.; globulin, +1; colloidal gold, 0000000000; mastic, 000000; and serology, negative. An electrocardiogram showed sinus tachycardia, small QRS complexes and flat T waves in lead I, and inverted T waves in leads II and III, suggesting myocardial changes. Electromyographic study disclosed fasciculations and fibrillations in all extremities. Chest roentgenogram disclosed minimal pneumothorax and an ill defined infiltration of the right apex of indeterminate etiology.

Course. The patient's weakness became rapidly worse and was not relieved by Tensilon or neostigmine. Increasing lung congestion was evident. Temperatures varied considerably, ranging from 96 to 102° F. rectally. Antibiotics were given. Dyspnea became severe. Cyanosis and ankle edema developed. He was too weak to eat, and tube feeding was begun. He was digitalized. He became progressively less responsive, lapsing into coma and dying on the eleventh hospital day.

Gross and microscopic general pathologic diagnoses. [1] Acute pulmonary edema with varying stages of acute and unresolved lobular pneumonia. [2] Fibrinopurulent pleuritis. [3] Recanalized thromboses in several pulmonary arteries. [4]

Dense fibrous tissue near the hilum of the lung showing anthracosilicosis and cystic spaces surrounded by foreign body giant cells. [5] Early degenerative fatty infiltration of the liver. [6] Brown atrophy of myocardial fibers and fibrous thickening of the epicardium. [7] Surgical removal of the thymus. [8] Advanced cachexia—weight 88 lb.

Nervous system. Gross observation: The brain weighed 1,540 gm. The meninges appeared normal. The basilar vessels were mildly atherosclerotic. Examination of the surface of the cerebral cortex, brain stem, cerebellum, sympathetic chains, and portions of the brachial and lumbosacral plexus disclosed no abnormality. Coronal sections of the brain were normal. The ventricular system was of normal size and shape.

The over-all size of the spinal cord was slightly reduced. Serial cross sections disclosed that this smallness was primarily due to shrinkage of the gray matter at all levels.

Microscopic observations: Sections were prepared by the following staining technics: hematoxylin-eosin, cresyl violet, van Gieson, Mallory trichrome, Weil and Luxol blue methods for myelin, and Hortega silver carbonate methods.

Spinal cord. The most striking abnormality was a marked reduction of anterior horn cells at all levels (Figs. 6 and 7). The majority of the remaining neurons were in varying stages of chronic degeneration with shrinking and hyperchromaticity of the nuclei. In many sections, no normal appearing anterior horn cells could be seen. The cervical and lumbosacral enlargements were affected to the same extent. The lateral portions of the anterior horn in the enlargements were possibly more atrophic than the medial portions, but the difference was probably not significant. Associated with these alterations in the anterior horn cells was a dense astrocytic gliosis of the entire anterior horn (Fig. 8).

An area was noted in the upper thoracic and cervical regions in the dorsomedial portion of the fasciculus gracilis which appeared slightly pale with Weil and Luxol blue methods for myelin. There was slight spreading of the nerve fibers in this area with clear spaces between, but the myelin sheaths appeared intact and Hortega silver carbonate preparations disclosed no axonal destruction or gliosis in the area.

Other areas of the white matter of the spinal cord, particularly the lateral and ventral corticospinal tracts, showed no abnormality with myelin or silver preparations (Figs. 9 and 10). The spinal meninges were normal.

Brain stem. The same chronic destructive neuronal changes with severe reduction in cell number that were noted in the anterior horn cells were evident in the nucleus ambiguus and the motor nuclei of the trigeminal, facial, and hypoglossal nerves (Fig. 11). The associated gliosis was also present in the abnormal nuclei. The dorsal motor

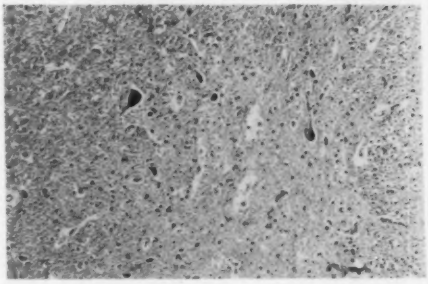

Fig. 6. Anterior horn in upper thoracic cord. Note reduction in number of neurons. Hematoxylin-eosin. Zeiss Planapochromat 25

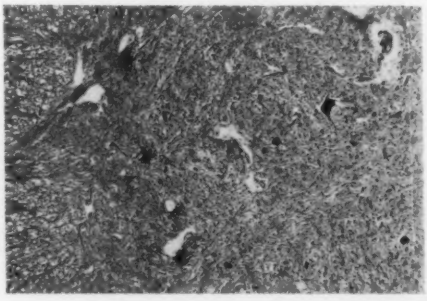

Fig. 7. Similar changes in anterior horn in the lumbar enlargement. Hematoxylin-eosin. Zeiss Planapochromat 25

Fig. 8. Note gliosis in anterior horn in the upper thoracic cord. Hortega silver carbonate. Zeiss Planapochromat 25

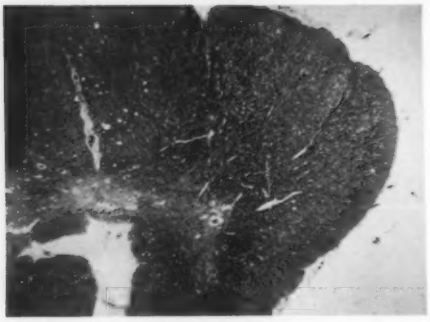

Fig. 9. Note normal white matter of the cord. Weil. Zeiss Achromat 2½

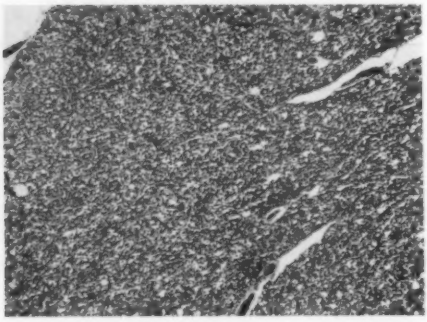

Fig. 10. High power view of area of the corticospinal tract in the thoracic cord showing no evidence of demyelination. Weil. Zeiss Apochromat 16

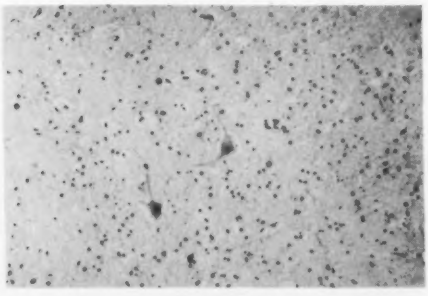

Fig. 11. Hypoglossal nucleus. Note marked reduction in the number of neurons. Cresyl violet. Zeiss Planapochromat 25

nucleus of the vagus and all sensory nuclei appeared normal. The oculomotor, trochlear, and abducens nuclei were also spared. Luxol blue and Weil myelin preparations showed no evidence of demyelination of the corticobulbar, corticospinal, or other long tracts of the mesencephalon, pons, or medulla (Fig. 12).

Cerebellum. The cytoarchitecture and myelinization of the cerebellum appeared normal.

Basal ganglia and thalamus. The configuration and cytoarchitecture were normal. The internal capsule showed no evidence of demyelination.

Cerebral cortex. The cytoarchitecture and myelinization were normal in sections obtained from frontal, temporal, parietal, and occipital cortex. In particular, the small and large pyramidal cells of the motor cortex were not decreased in number or abnormal in appearance.

Blood vessels. Mild atherosclerotic changes were evident in cerebral and spinal vessels. Otherwise they were normal.

Peripheral nerves. Sections of lumbosacral and brachial plexus were prepared with Hortega silver carbonate stains and hematoxylin-eosin. Far advanced chronic degenerative changes were noted. The nerve fibers were greatly reduced in number, and the remaining few showed swollen sheaths of Schwann. The degenerated nerve fibers were replaced by connective tissue (Fig. 13).

Sympathetic chain. Hortega silver carbonate preparations of the sympathetic trunk were normal.

Muscles. Sections were obtained from the posterior neck muscles and biceps, psoas, pectoralis major, temporalis, diaphragm, and mid-dorsal paravertebral muscles. Sections were prepared with hematoxylin-eosin, van Gieson, and Mallory trichrome methods. Although varying in severity, the pathologic alterations were similar in all muscles. There was extensive replacement of muscle by fat and connective tissue, and, in some sections, only a few remaining degenerating muscle fibers could be seen. In other areas, definite groups of small muscle fibers were observed interspersed with more normal appearing muscle fibers. Many of the smaller fibers were under 10 μ in diameter. The larger fibers appeared normal. Thus, the findings were typical of neurogenic atrophy of muscle except in the areas so severely destroyed that they could not be adequately assessed.

SUMMARY AND CONCLUSIONS

1. Histories are presented of 3 brothers who developed a very slowly progressive spinal and bulbar muscular atrophy in the fifth and sixth decades; 2 are living in the ninth and tenth years of their illness. The third patient died in the fifteenth year of his disease.

2. Clinical findings disclosed only lower motor neuron involvement.

3. Necropsy disclosed severe degenerative

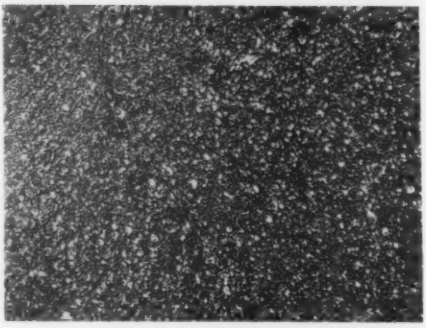

Fig. 12. High power view of portion of medullary pyramid. Note normal myelinization. Weil. Zeiss Planapochromat 25

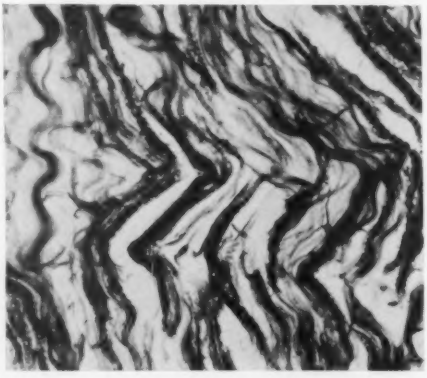

Fig. 13. Brachial plexus. Note reduction in number of nerve fibers and replacement by connective tissue. Hortega silver carbonate. Zeiss Planapochromat 40

changes of the anterior horn cells throughout the length of the cord and similar chronic degenerative changes in the motor portion of the trigeminal nucleus, the nucleus ambiguus, and the facial and hypoglossal nuclei. The corticobulbar and corticospinal tracts appeared normal.

4. The most probable mode of inheritance in this family is an autosomal or sex-linked recessive. Nuclear amyotrophies in adults showing a hereditary tendency are usually transmitted as a dominant.

5. Primarily because of the different prognosis, it would seem advisable, clinically, to separate progressive spinal muscular atrophy from amyotrophic lateral sclerosis.

The author is indebted to Dr. Konstantin Scharenberg, Director of the Neuropathology Laboratory, University of Michigan, for helpful advice and permission to utilize the facilities of his laboratory for this study and to Dr. Russell N. DeJong for suggestions and criticisms.

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Relation of Millipore to healing and regeneration in transected spinal cords of monkeys

James B. Campbell, M.D., and William F. Windle, Ph.D., Sc.D.

REGENERATION IN THE transected spinal cord, long considered virtually impossible, does occur under favorable conditions.[1] Structural and functional restitution is less of a problem in fishes and amphibians than it is in mammals. The concept of axonal regeneration across a gap resulting from complete severance of the mammalian spinal cord has been controversial because results of experiments devised to demonstrate a regenerative potential have been so variable. It has been pointed out[1, 2] that failure in the past to obtain recognizable central neural regeneration may have been due to casual experimentation without the advantage of surgical technics developed to minimize tissue damage and attendant scarring. Furthermore, improper timing of experiments and inadequate histologic methods may have contributed to negative results. One of the principal drawbacks has been lack of means of creating and maintaining a milieu favorable for longitudinal orientation of sprouting axons and preventing the development of scar tissue at the site of regeneration. If favorable conditions can be met consistently, anatomic union that may modify the paraplegic state[3] can be anticipated.

Cats with severed spinal cords ensheathed by Millipore have exhibited remarkable healing, and regenerating intraspinal neurons have bridged gaps of several millimeters.[4, 5] Similarly, long gaps in peripheral nerves have been traversed.[6] It was hoped that equally successful results might be achieved in the spinal cords of monkeys. Earlier studies on the spinal cords of monkeys had shown that regenerating nerve fibers which succeeded in traversing the region of cord transection were subsequently blocked by scar tissue formation and degenerated before effecting functional connections.[7] The present experiments were designed to test the efficacy of the porous Millipore tubulation technic successfully employed in cats.[8]

MATERIAL AND METHODS

Sixteen monkeys of the species *Macaca cynomolgus* comprised the experimental series listed in Table 1. After performing a laminectomy under intravenous Nembutal anesthesia, the dura mater was incised longitudinally. The dorsal spiral vein was doubly ligated in most instances and the spinal cord transected between the ligatures at the level of the dentate ligaments. The ventral spinal artery was spared in 9 of the operations. A sheet of Millipore* was passed beneath the cord in the subdural space and the ends brought together, folded, and clipped in order to form a sheath. The size of the gap varied from 2 to 6 mm. and, in most instances, was 4

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Presented at the Section of Neuroanatomical Sciences, American Academy of Neurology, April 16, 1959, at Los Angeles. This study was supported by Army Medical Service, Research and Development Command, Office of the Surgeon General under contract number DA-49-007-MD-545, and grants from National Institutes of Health, B-1723, and United Cerebral Palsy Research and Educational Foundation, Inc., R-60j-F58c.

*Millipore Filter Corporation, Watertown, Mass.

TABLE 1
SUMMARY OF OPERATIONS

Monkey			Operation				
No.	Sex	Weight (kg)	Laminectomy (no. spaces)	Artery*	Veins*	Transection	Stitch	Duration (days)
1	male	4.8	3	cut	cut	T9	none	4†
2	female	2.1	5	cut	tied	T10	placed	4†
3	female	2.4	?	spared	cut	T9	none	5
4	female	2.9	4	spared	tied	T11	none	7
5	female	2.4	4	spared	tied	T11	none	14
6	male	6.2	5	spared	cut	T7	placed	20
7	male	5.3	3	spared	tied	T10	none	21
8	female	2.6	5	cut	tied	T11	placed	27†
9	male	6.8	5	spared	tied	T8	placed	28
10	female	3.8	4	spared	tied	L1	none	35
11	male	4.9	5	cut	cut	T3	placed	42
12	male	4.8	5	spared	tied	T6	placed	56†
13	female	2.6	4	spared	tied	T7	none	69†
14	male	5.2	5	cut	tied	T11	placed	80
15	female	1.8	3	cut	tied	L1	placed	110
16	male	6.0	5	cut	cut	T9	none	118†

*Refers to ventral spinal artery and dorsal spinal vein
†Animals found dead. All others killed at times indicated

mm. in length. A 3-mm. gap can be seen through the translucent Millipore in Figure 1D. A single sling stitch of Silicone-coated silk† spanned the gap in one-half of the experiments. No effort was made to approximate the stumps of the cord, and this suture was tied without tension. In several of the experiments in which the ventral spinal artery was spared, the Millipore sheath passed dorsal to the artery as is indicated in Figure 1C. Bilateral pudendal neurectomy was performed at the same time to facilitate evacuation of the bladder and bowel.

The animals were placed in metal cages on sponge rubber mattresses encased in soft cloth. Daily bladder and bowel care was given and the bedding was changed as often as it became soiled. Preoperative and postoperative motion picture photographs were taken at four days, seven days, and weekly thereafter. The animals survived for four to one hundred eighteen days, and, in most instances, were killed by intracardiac perfusion-fixation, using formalin and gum acacia.[9] The appropriate region of the spinal cord was removed and prepared for histologic study by the Protargol method of Bodian. The spinal cords of monkeys 1 and 2 were stained by Mallory's phosphotungstic acid hematoxylin technic. All specimens were sectioned serially in parasagittal planes.

No Millipore was applied to the severed cords of monkeys 1 and 7. These and 5 other monkeys of the genus M. cercopithecus to which Millipore was not applied and which were killed one hundred forty to one hundred sixty-three days after spinal cord section during earlier experiments[7] served as controls.

RESULTS AND COMMENTS

Monkeys with transected spinal cords were more active than cats with severed spinal cords. Some engaged in spontaneous movement in the cages. They were handled at least once daily to keep them clean. All of this resulted in excessive motion of the back at the site of the laminectomy, and this was reflected in the appearance of the histologic preparations. The Millipore sheath appeared to have moved from its initial position in several instances and had slipped away from the caudal stump of the severed spinal cord in one.

The sheath, although initially placed quite loosely around the cord (Fig. 1), exerted some pressure on the stumps, presumably at the height of the postoperative swelling. The resultant pressure necrosis added to ischemic

†Dow Corning Corporation, Midland, Mich., and the Surgical Products Division of American Cyanamid Company, Danbury, Conn.

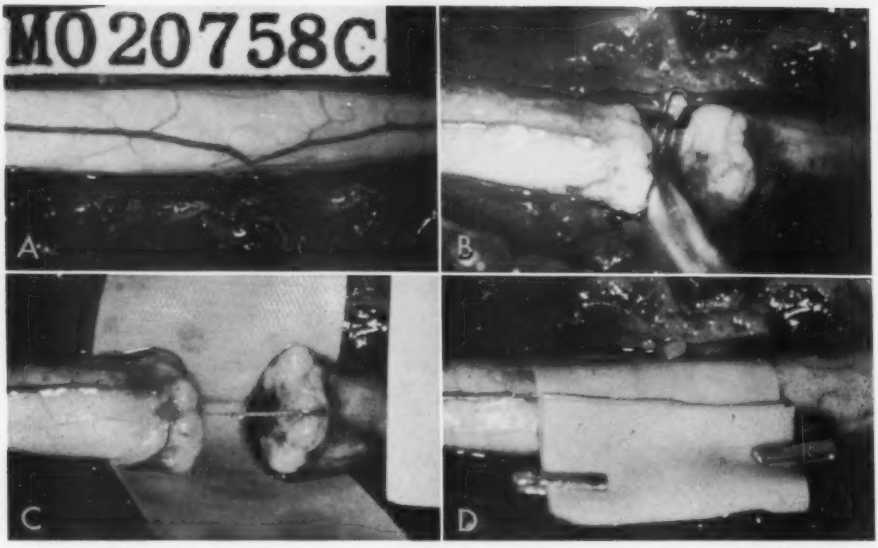

Fig. 1. Stages of the surgery on monkey 6. A Zeiss otoscope was used for photography at the operating table. Rostrad is to the left. (Approximately X3.)

changes in either stump led to partial tissue degeneration for a variable distance cephalad and caudad from the transection. Varying degrees of cavitation were associated with the necrosis.

The most favorable preparations exhibited some of the characteristics described after employment of this technic in the severed spinal cord of the cat.[4,5,8] Cells, presumably from indifferent or dedifferentiated connective tissue cells, appeared to have migrated quite early along the inner surface of the Millipore sheath from the opposing stumps of the spinal cord. Within three weeks, there were many cells in the intervening clot of plasma and blood, but their orientation was at random. Longitudinal orientation of cells seemed to be limited to the immediate vicinity of the internal surface of the Millipore sheath.

The least satisfactory specimens were those in which the Millipore had slipped, large blood clots had formed, or a considerable amount of pressure necrosis had taken place. In one instance, integrity of the Millipore was not maintained because of mechanical rupture, with the result that cells grew over the stumps and the gap was filled with randomly oriented scar tissue.

Orientation of tissues during healing under good conditions is illustrated in Figure 2A in contrast to a specimen of similar age around which no Millipore was placed (Fig. 2B). The apparent restitution of structural continuity seen twenty-one days postoperatively in Figure 2A was due to a well-oriented outgrowth of cells and capillary blood vessels. No distinct boundary between the gap and spinal cord stumps was visible in this specimen. A few sprouting neurons were seen in the region of the gap, but none bridged the transection completely.

In a monkey twenty-eight days after operation, central nerve fibers were encountered in the stumps near the gap but did not cross the gap. These fibers were collected in loose fascicles containing elongated nuclei of cells of undetermined character. Figure 3A illustrates the longitudinal orientation existing there. It was clear that many of the fibers were retained neurons of the stump rather than regenerated

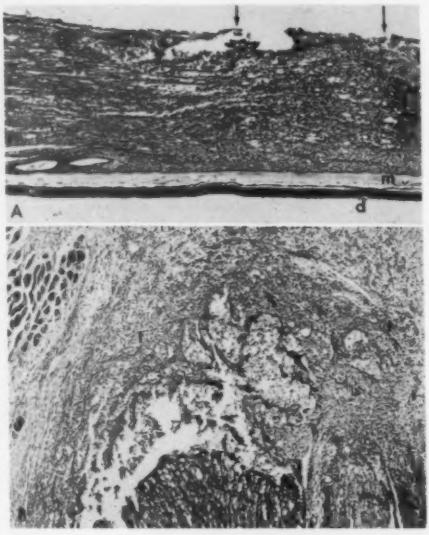

Fig. 2. [A] Spinal cord transaction of monkey 6, in which the gap is undergoing a well-oriented organization within the Millipore sheath (*m*) and dura (*d*) is indicated by arrows. [B] No Millipore was used in monkey 7 of similar age, and cord stump (*s*) is shown capped by scar tissue (*t*). (Protargol stain, X30.)

neurons. It is interesting to follow the development of these fascicles in later stages. Within eight weeks, there appeared to be numerous regenerating nerve fibers among them. Furthermore, the fascicles had a tighter organization, although the tissue between them was more openly arranged than earlier, as is shown in Figure 3B.

As this process continued, the character of the fascicles changed. After seventeen weeks, they had become encapsulated by tissue resembling the perineurium of peripheral nerve bundles. They were no longer constituted by retained intraspinal neurons only but appeared to be formed largely by new axons. Their nerve fibers were small, and the bundles resembled peripheral autonomic nerves. Figures 4A and B show these fascicles cut longitudinally and transversely. Cells with elongated nuclei were associated with the nerve fibers of these fascicles. These resembled the neurilemma, or Schwann cells, of peripheral nerves. The fascicles were traced back into the spinal cord where they were continuous with intact portions of the lateral and ventral funiculi. They were found throughout the gap region, but their fibers did not cross the gap. The spinal lesion had been organized into a fibrous scar, with random orientation of elements, among which the fascicles of nerve fibers wandered about. Had the tissue become well oriented in the gap, it is possible that these neurons would have grown across the gap. Further experiments may provide the answer.

DISCUSSION

Little space need be devoted to discussion of the observations in this series of monkeys. No gap was bridged by neurons, and, of course, no improvement occurred in the neurologic status of the animals. Nevertheless, we do not

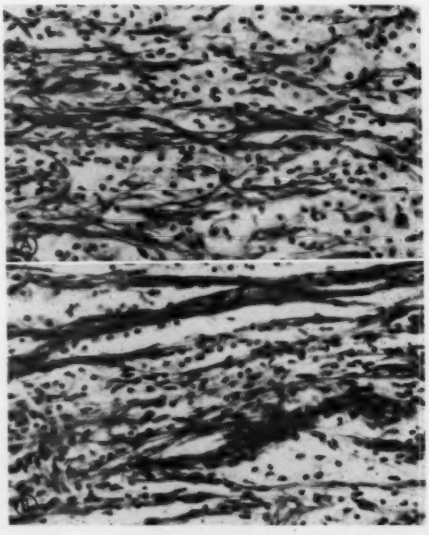

Fig. 3. [A] Nerve fibers coursing along cellular strands in a spinal cord stump of monkey 9. These appear to be persisting fibers, but sprouts are growing from them. [B] Fascicles are forming near the junction of scar and stump in monkey 12. (Protargol stain, X300.)

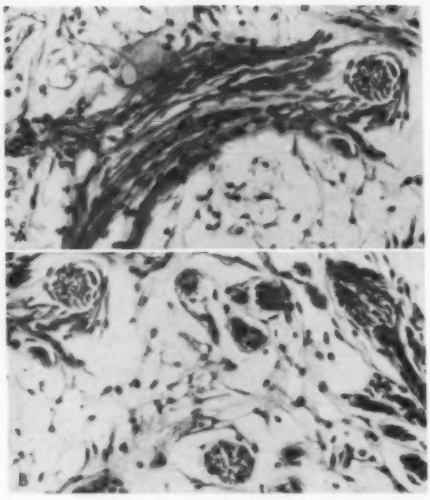

Fig. 4. Fascicles of regenerated central nerve fibers in scar at the site of transaction of spinal cord of monkey 16. These arise in the ventral and lateral funiculi of the rostral stump. [A] The nuclei of cells resembling neurilemma are seen in the bundles sectioned longitudinally. [B] Fine nerve fibers in bundles can be seen. (Protargol stain, X300.)

consider the experiments unsuccessful. We learned that satisfactory orientation of cellular growth within the Millipore sheath depends on mechanical stability at the operative level and, under the most favorable circumstances, appears to be similar to that in the cats. This is a step forward.

Intraspinal neurons in the monkey did exhibit regenerative potentialities. Not only were sprouts seen three weeks after operation, but a substantial later outgrowth was in progress seventeen weeks postoperatively. This outgrowth of fibers from the stumps of the severed cord presented an unusual appearance suggestive of some postcompression observations of Duncan[10] in the study of the rat's spinal cord and certain findings in man reviewed by Druckman.[11] It should not be surprising that central spinal neurons take on the appearance of peripheral nerve fibers when they leave the spinal parenchyma and enter a region of connective tissue. Primary motor neurons leaving the spinal cord do this normally. The question may arise: Once regenerated and transformed to peripheral neuron types, can the fibers grow back into the central nervous system, for example, into the other stump of the cord? The answer is probably "Yes." Peripheral nerves have been observed to grow into the brain when implanted under favorable conditions.[12] Recently, dorsal root axons have been observed reentering the cord after they had been severed and repaired by the Millipore tabulation technic;[13] and, indeed, action potentials were recorded some distance up the cord by stimulating the roots peripheral to the point of severance.[14] If only a few descending axons succeed in crossing the gap and establishing connections, will motor function be restored? Cats with no more than 5 or 10 per cent of the fibers of the ventral funiculi remaining after subtotal transections were able to walk.[15]

The outlook for functional recovery after spinal cord section is better than ever before. Millipore unquestionably provides a method to control scar formation while allowing nutrition of the tissues in the initial stages of the recovery from surgical trauma.[8] Nevertheless, caution must be exercised in drawing conclusions from experiments unless all conditions are controlled. It may be well at this stage to try to agree on the experimental conditions that must be satisfied before claims of success can be established.

In the first place, there must be proof that the spinal cord was severed completely. Next in order come the clinically observable signs of restitution of motor and/or sensory functions. But, one must not halt there. Physiologic proof of conduction across the healed lesion, with electrical recording from the spinal cord following stimulation above or below, must be presented. Transsynaptic potentials likewise need to be demonstrated. Finally, there must be unquestionable verification of reestablishment of histologic continuity. All of these conditions must be observed in one and the same animal if regeneration in the spinal cord is to be considered successful. No experiments to our knowledge have met all of these requirements.

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Studies in febrile seizures

II. Febrile seizures and the balance of water and electrolytes

J. Gordon Millichap, M.D.

In an initial study concerning the factors involved in the induction of febrile seizures, a threshold dependent upon the height of the body temperature was demonstrated in children with recurrent seizures and in laboratory animals subjected to hyperthermia.[1] The temperature at onset of clonus, or threshold convulsive temperature, in animals was independent of the intensity and duration of the heating stimulus and of the rate of rise of body temperature. In mice, the rate of rise of temperature could be varied over a wide range while the threshold convulsive temperature remained constant. In 2 groups of kittens that convulsed in response to stimuli of weak and strong intensity, the rapidity of rise of temperature differed significantly while the convulsive temperature was unaltered. Further, a constant convulsive temperature was observed in animals in which the rate of rise of body temperature was retarded by means of chlorpromazine. The body temperature at onset of clonus was employed as an index of the febrile seizure threshold in the present study concerning the relation of the balance of water and electrolytes to the mechanism of fever-induced seizures.[2]

That brain excitability may be modified by changes in the distribution of water and electrolytes has been demonstrated in children subject to grand mal seizures[3] and in animals with seizures induced by electroshock stimuli.[4] Lennox[5] has alluded to the possible importance of hydration and the permeability of cell membranes in the mechanism of febrile seizures. In cats subjected to hyperthermia, Yannet and Darrow[6] observed a shift of water unaccompanied by cations from the cells to the extracellular fluid of the brain. These authors concluded that the alteration in the distribution of water could not be correlated with the occurrence of febrile seizures but that such a relationship was a most suggestive possibility.

In the present investigation, the changes in the threshold to febrile seizures observed in relation to age were associated with concomitant changes in the concentration and distribution of water and electrolytes in the brain. The increased susceptibility of young animals to febrile seizures appeared to be related to certain peculiarities of the balance of water and electrolytes in the immature brain. The results obtained in these developmental studies were supported by further observations in mature animals. In contrast to previous experiments in which animals were exposed to lethal and prolonged hyperthermia, in the present study the threshold to seizures was measured and the application of the fever stimulus was short; the chemical determinations were performed in control animals not subjected to hyperthermia, and the complicating effects of fever and of the convulsion per se on the distribution of electrolytes were avoided.

PROCEDURES AND METHODS

Newborn, 1-month-old, and adult rats of the Holtzman and Sprague-Dawley strain and Swiss albino mice, 2 to 3 weeks of age and 15 to 20 gm. in weight, were used as experimental animals. Hyperthermia was induced by means of a microwave diathermy generator,

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This work was supported by Grant B-1627 from the National Institute of Neurological Diseases and Blindness and a grant from Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.

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according to the method described in a previous communication.[1] Body temperature was recorded initially and at onset of clonus with a telethermometer and a thermistor hypodermic probe inserted into the deep subcutaneous tissue of the back. The Fahrenheit rather than centigrade scale of this instrument was employed because of the greater precision of measurement possible. The duration of application of the hyperthermic stimulus was timed, and the rate of rise of temperature was calculated.

The threshold convulsive temperature was determined in groups of rats of different ages, each group containing 8 to 15 animals. Rats in Groups 1, 2, and 3 were 4 to 7 days, 28 to 32 days, and 55 to 65 days of age, respectively; rats in Group 4, of the same age and strain as those in Group 3, were given an intraperitoneal injection of 5.5% glucose solution, 10 cc. per 100 gm. of body weight, at an interval of four hours before testing with the fever stimulus.

The concentrations of water and electrolytes in plasma and brain tissue were estimated in 4 groups of rats of the same age and strain and, when possible, of the same litters as those used for determination of the febrile seizure threshold. The methods of analyses were those employed in a parallel study of the chemical composition of the brain and the threshold to electroshock seizures in young animals.[7] Animals were killed by decapitation, blood was collected in tubes that contained heparin, and the cerebral cortex and subcortical white matter were transferred to tarred beakers, after removal of macroscopic blood and surface vessels. The numbers of samples obtained for separate analyses from newborn, 1-month-old, and adult rats were 18, 11, and 5, respectively; each sample for each set of determinations consisted of the pooled specimens from 8 to 10 newborn rats, 4 1-month-old rats, and 3 adult rats. Plasma and brain tissue were dried at 105° C. to a constant weight; the water content was calculated from the difference between wet and dry weights. Nitric acid was added to the dried tissues, which were digested by gentle heating; the resulting solutions were analysed for sodium and potassium by means of a Process and Instruments flame-photometer with an internal lithium standard. Tissue chloride determinations were performed by the method of Van Slyke and Sendroy[8] and plasma chloride determinations, by the method of Schales and Schales.[9] In calculations of the cellular concentrations of water, sodium, and potassium, the chloride space was used as a measure of the extracellular fluid volume in the brain.[10] As a method for the estimation of absolute values, the limitations of the chloride space are recognized but, as a measure of relative values and of the direction of changes induced experimentally, objections to the method might be lessened. In order to make possible the determination of standard errors of the data on water and electrolytes for comparative purposes, the calculation of concentrations of intracellular cations was made for each sample rather than using the mean values obtained for each group of animals.

At random, 40 mice, 3 to 4 weeks of age, were divided into 4 equal groups and 20 mice, 2 to 3 weeks of age, into 3 groups; 1 group from each set of animals was used as a control. The remainder were treated by methods known to modify the balance of water and electrolytes as follows: Group 1 was deprived of water for two days to produce dehydration and an increase in the concentration of extracellular electrolytes; Group 2 received 5.5% glucose solution by intraperitoneal injection, 2 doses of 10 cc. per 100 gm. of body weight at an interval of one hour, to cause depletion of extracellular electrolytes and cellular hydration;[4,11] Group 3 received 0.85% sodium chloride solution in the same dose and by the same route as the animals in group 2 to cause expansion of the extracellular fluid volume without alteration of the cell volume or concentration of electrolytes;[12] Group 4 was given acetazoleamide, 60 mg. per kilogram orally, which is reported to modify the concentration and distribution of sodium and potassium in the brain;[13,14] and Group 5 received diphenylhydantoin sodium, 50 mg. per kilogram orally, reported to modify the balance of sodium without alteration of the cellular concentration of potassium.[13] All animals were subjected to hyperthermia, and the temperature at the onset of generalized clonus was recorded in those that convulsed. Mice treated with parenteral solutions (Groups 2 and 3) were tested at one hour after the second

injection; those given acetazoleamide and diphenylhydantoin were tested at three hours after administration of the drug, which is the approximate time of the maximal effect on the metabolism and excitability of the brain.[13-15] In this study and in that performed in rats, the control animals were maintained in the same environment and were tested within five to forty-five minutes of the experimental animals. All determinations of the threshold to febrile seizures were made between noon and 4 P.M., so that a possible variability in response related to the time of day was excluded.

The concentration of carbonic anhydrase in the brain of 12 mice subjected to fever-induced seizures was compared with the concentration in an equal number of control animals. The test animals were killed by decapitation immediately after the febrile seizure. Macroscopic blood was removed from the brain, and the cerebral cortex and subcortical white matter were homogenized with 0.85% sodium chloride solution, in a dilution of 1 in 10. The carbonic anhydrase activity of the supernatant fluid was determined after centrifugation by the manometric method of Meldrum and Roughton.[16] The enzyme activity in contaminating red cells was estimated in a previous study and was found to be less than 1% of that in the brain tissue.[17]

Histologic sections were prepared from the brain of rats 1, 14, and 35 days of age and of adult rats.

RESULTS

Febrile seizure threshold in rats. Table 1 shows the febrile seizure threshold in newborn, 1-month-old, and adult rats and in adult rats treated with 5.5% glucose solution. A significant elevation in the threshold convulsive temperature with increasing age was apparent when the values obtained for the newborn and older animals and for older and adult animals were compared; a significant reduction in the threshold was observed in adult animals treated with glucose solution. The newborn and older rats with relatively low seizure thresholds recovered, whereas the untreated adult rats with a high threshold died after convulsion. In glucose-treated rats that convulsed at a lower temperature, the postictal mortality was only 25%.

Analyses of water and electrolytes in rats. Table 2 shows the concentrations of water and electrolytes in the plasma and brain of newborn, 1-month-old, and adult rats and of adult rats treated with 5.5% glucose solution. In Figures 1, 2, 3, and 4, the direction of changes in total, intracellular, and extracellular concentrations of water and electrolytes in the brain is compared with that of the febrile

TABLE 1

FEBRILE SEIZURE THRESHOLD IN YOUNG AND ADULT RATS

Age of rat	*Weight in gm.*	*No. of rats*	*Threshold convulsive temperature in degrees F. Mean ± standard error*	*Significance of differences* $M_1 - M_2$	*df*	*P value*
Newborn (4-7 days)	10- 16	12	106.8 ±0.21	3.7	25	<0.05
Older (28 days)	64- 72	15	110.5 ±1.56	5.0	19	<0.001
Adult (55-65 days)	95-104	6	115.5 ±0.24	2.9	12	<0.001
Adult Glucose-treated	99-110	8	112.6 ±0.28			

$M_1 - M_2$: difference between means in °F.
df: degrees of freedom $= N_1 + N_2 - 2$
P obtained by the Fisher "t" test.

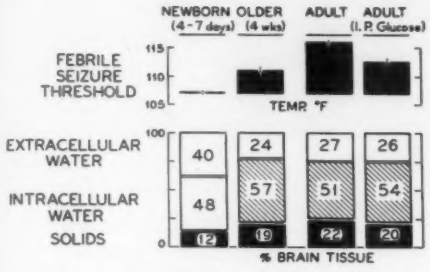

Fig. 1. Febrile seizure threshold in rats of 3 different age groups and in adult rats given 5.5% glucose by intraperitoneal injection in relation to volume and distribution of water in the brain

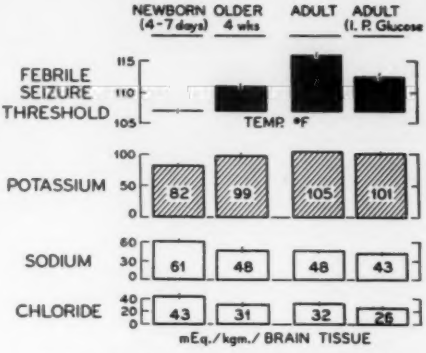

Fig. 2. Febrile seizure threshold in rats of 3 different age groups and in adult rats given 5.5% glucose by intraperitoneal injection in relation to concentrations of electrolytes in the brain

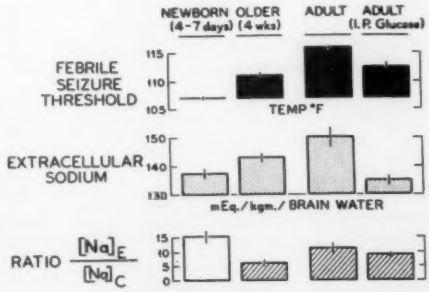

Fig. 3. Febrile seizure threshold in rats of 3 different age groups and in adult rats given 5.5% glucose by intraperitoneal injection in relation to concentration of extracellular sodium and ratio of extracellular to intracellular sodium in the brain. Extracellular sodium concentration is calculated in terms of extracellular brain water.

seizure threshold. Tables 1 and 2 show the details of these data and the significance of the changes that occur with age and of those induced experimentally; the values obtained for newborn and older rats, older and adult rats, and adult and glucose-treated adult rats are compared. The concentrations of water and electrolytes are those of normothermic control rats of the same age and strain as the rats used for estimations of the febrile seizure threshold.

The low threshold to febrile seizures in newborn and 1-month-old rats was associated with relatively low concentrations of extracellular sodium and of total potassium in the brain. When the values obtained in 1-month-old and adult rats were compared, the relatively low seizure threshold in the younger animals was associated with significant differences in the balance of water and electrolytes. In the brain, total water content, volume of intracellular water, and concentration of extracellular potassium were elevated; volume of extracellular water, concentration of total potassium and intracellular potassium, ratio of intracellular to extracellular potassium, and ratio of extracellular to intracellular sodium were lowered. In the plasma, concentration of sodium was lowered.

The lowered threshold to febrile seizures in the glucose-treated adult rats was associated with the following significant changes. In the brain, total water content, volume of intracellular water, and concentration of extracellular potassium were elevated; concentration of total sodium and extracellular sodium, concentration of total potassium and intracellular potassium, and ratio of intracellular to extracellular potassium were lowered. In the plasma, concentration of potassium was elevated and concentration of sodium was lowered.

Febrile seizure threshold in mice. In Table 3, the febrile seizure threshold in test animals

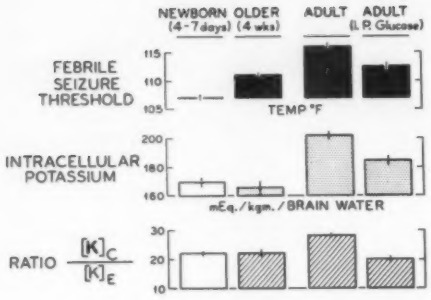

Fig. 4. Febrile seizure threshold in rats of 3 different age groups and in adult rats given 5.5% glucose by intraperitoneal injection in relation to concentration of intracellular potassium and ratio of cellular to extracellular potassium in the brain. Intracellular potassium concentration is calculated in terms of intracellular brain water.

is compared with that of controls. The seizure threshold was elevated in mice deprived of water and dehydrated, was lowered by intraperitoneal injection of 5.5% glucose in water, and was unaltered by injection of 0.85% sodium chloride solution. In mice treated with acetazoleamide, the seizure threshold was elevated, whereas in those given diphenylhydantoin the threshold was lowered but not significantly. In a subsequent experiment in which larger doses of diphenylhydantoin were administered to mice, the febrile seizure threshold was reduced significantly and the degree of reduction was related to the dose.[18] The febrile seizure was exacerbated by diphenylhydantoin. Changes in concentrations of water and electrolytes induced by these experimental procedures have been reported,[4,11-14] and the determinations were not repeated in this experiment.

Activity of brain carbonic anhydrase. Table 4 shows the activity of brain carbonic anhydrase in mice subjected to febrile convulsions and in control animals. The brain enzyme activity was not impaired by the degree of hyperthermia required to induce the febrile seizure.

Histologic maturation of the rat brain. Figure 5 shows the histologic changes in the brain of rats during development. The cortex of the newborn brain was characterized by relatively dense collections of neurons of small size; Nissl substance and glial satellites were absent. Axons and dendrites were observed in sections at 14 days, but myelinization was present only in the brain examined at 35 days and in adult brain.

DISCUSSION

The height of the fever as an index of the seizure threshold has proved of value in the present investigation of factors involved in the mechanism of febrile seizures. The elevation of the threshold to febrile seizures which occurs with increasing age was associated with developmental changes in the balance of water and electrolytes. The significance of certain of these changes in relation to the heightened susceptibility of young animals to febrile seizures was corroborated by the studies in adult animals in which the threshold was lowered experimentally by the induction of changes in the concentration of water and electrolytes.

The threshold to febrile seizures in rats was related inversely to total water content, volume of intracellular water, and concentration of extracellular potassium in the brain. The threshold was related directly to concentration of extracellular sodium, concentration of total potassium and intracellular potassium, and ratio of intracellular to extracellular potassium in the brain. It was related directly to concentration of sodium in the plasma. These findings were supported by the results of experiments in mice in which the febrile seizure threshold was modified by methods known to alter the balance of water and electrolytes.

Water balance. In previous studies, Darrow and Yannet[11] observed that the depletion of extracellular electrolytes produced by the intraperitoneal injection of 5.5% glucose solution in cats was accompanied by a decrease in the extracellular fluid volume and an increase in the intracellular fluid volume of liver and muscle tissue. In brain, no change in total water or distribution of water was found, and it was concluded that brain cells adjust to extracellular electrolyte depletion by the release of intracellular potassium. All tissues were removed for analyses at an interval of twenty-four hours after the experimental pro-

TABLE 2

WATER AND ELECTROLYTE COMPOSITION OF PLASMA AND BRAIN OF RATS*

Age of animal	Concentrations of water and electrolytes									
	PLASMA					CEREBRUM				
	No. of Samples	H_2O	Na	K	Cl	No. of samples	H_2O	Na	K	Cl
		%	mEq/kg/plasma				%	mEq/kg/wet tissue		
Newborn rat (4-7 days)	18[1]	94.89 ±.32†	135.9 ±1.7	7.68 ±.21	98.33 ±1.54	27[1]	87.61 ±.16	61.45 ±.58	82.43 ±.56	43.02 ±.75
P_1 values		<.01	N.S.	N.S.	<.001		<.001	<.001	<.001	<.001
Older rat (28-32 days)	11[2]	93.40 ±.28	139.0 ±1.3	7.40 ±.20	114.5 ±2.2	11[2]	81.30 ±.71	47.90 ±1.03	99.20 ±1.89	30.80 ±.68
P_2 values		<.01	<.05	N.S.	<.001		<.01	N.S.	<.02	N.S.
Adult rat (55-65 days)	5[3]	92.10 ±.18	143.7 ±1.4	6.97 ±.06	101.5 ±.5	5[3]	78.30 ±.40	48.00 ±.43	104.5 ±.5	31.60 ±.89
P_3 values		<.01	<.001	<.02	<.001		<.02	<.001	<.05	<.001
Glucose-treated adult rat (55-65 days)	5[4]	90.40 ±.30	128.8 ±2.4	8.98‡ ±.65	86.40 ±2.46	5[4]	79.50 ±.10	43.10 ±.67	101.0 ±1.2	26.10 ±.44

* Normothermic rats of the same age and strain as those used for estimations of the febrile seizure threshold. Data used in part in parallel study of the relation of brain electrolyte metabolism to the threshold to electroshock seizures.[7]

[1], [2], [3], [4], Each sample represents pooled specimens of plasma or brain obtained from 10, 4, 3, and 3 animals, respectively.

P_1, P_2, P_3: Tests of significance for differences between newborn and older rats, older and adult rats, and adult and glucose-treated adult rats, respectively; values obtained by the Fisher "t" test.

† Mean ± standard error ‡ High values not explained by obvious hemolysis

Age of animal	Distribution of water and electrolytes in cerebrum							
	WATER		SODIUM			POTASSIUM		
	Intracellular	Extracellular	Extracellular	Intracellular	Ratio†	Intracellular	Extracellular	Ratio†
	% whole tissue		mEq/kg water			mEq/kg water		
Newborn rat (4-7 days)	47.30 ±1.36	40.20 ±1.48	137.5 ±1.9	15.15 ±3.28	15.45 ±2.73	169.0 ±3.5	7.76 ±.23	22.00 ±.62
P_1 values	=.001	<.001	<.05	N.S.	<.01	N.S.	N.S.	—
Older rat (28-32 days)	57.20 ±1.44	24.20 ±.93	143.0 ±1.4	22.10 ±2.27	6.46 ±.67	165.3 ±6.3	7.50 ±.22	22.00 ±1.04
P_2 values	<.01	<.01	<.01	<.01	=.02	<.001	<.02	<.001
Adult rat (55-65 days)	50.80 ±.77	27.60 ±.65	149.8 ±1.6	13.20 ±1.27	10.90 ±1.56	202.1 ±2.7	7.25 ±.06	27.90 ±.51
P_3 values	<.05	N.S.	<.001	N.S.	N.S.	<.01	<.05	<.01
Glucose-treated adult rat (55-65 days)	53.40 ±.62	26.10 ±.59	135.2 ±2.0	12.66 ±2.47	8.94 ±.91	185.2 ±4.1	9.44 ±.82	20.20 ±1.62

† Mean of ratios obtained from individual samples.

TABLE 3

MODIFICATION OF THE FEBRILE SEIZURE THRESHOLD IN MICE

Group number	Number of test animals	Treatment	Threshold convulsive temperature in degrees F. Test	Control	Difference	Significance of difference df	P value
1	9	Water deprivation†	112.0* ±.28	111.0 ±.28	+1.0	17	<0.05
2	9	Glucose intraperitoneally, 5.5%	109.7 ±.35	111.0 ±.28	−1.3	17	<0.01
3	9	Sodium chloride, 0.85%	110.7 ±.20	111.0 ±.28	−0.3	17	>0.30 (Not significant)
4	6	Acetazolamide, 60 mg. per kg.	112.4 ±.75	109.7 ±.59	+2.7	10	<0.02
5	6	Diphenylhydantoin, 50 mg. per kg.	108.5 ±.68	109.7 ±.59	−1.2	10	>0.20 (Not significant)

*Mean ± standard error †Animals lost 20% of their body weight.
df: degrees of freedom = $N_1 + N_2 - 2$. P value obtained by Fisher "t" test.
Mice in Groups 1, 2, and 3 were older than those in Groups 4 and 5, and the threshold temperature was correspondingly higher in control animals.

cedure. Swinyard[4] employed this technic subsequently to determine the effects of changes in the distribution of water and electrolytes in the brain on the electroshock seizure threshold in rats. Analyses of plasma and brain tissue were performed within the first four hours after the glucose injection, since the seizure threshold to electroshock was reduced markedly at this time and had returned toward normal in twenty-four hours. With this modification of the experimental procedure, Swinyard observed a significant increase in brain cell volume when the reduction in seizure threshold was maximal.

With few exceptions, factors that influence the threshold to electroshock seizures have been found to modify the febrile seizure threshold. The heightened susceptibility to fever-induced seizures of 1-month-old compared with adult rats was related to the cellular hydration of the brain but was independent of the volume of extracellular water. The

TABLE 4

ACTIVITY OF BRAIN CARBONIC ANHYDRASE IN MICE SUBJECTED TO FEBRILE SEIZURES

Group of mice	Number of specimens	Brain carbonic anhydrase units/gm./wet weight Mean ± standard error	Test of significance $M_1 - M_2$	P value
Controls (unheated)	6	258 ±10	5	>0.5 (Not significant)
Fever-induced seizure†	6*	253 ±35		

$M_1 - M_2$: difference between means in units
P value obtained by the Fisher "t" test.
†Degree of fever, 110-111 F.
*Each specimen obtained from the pooled brains of 2 animals that were killed by decapitation immediately after the seizure.

lack of correlation with the degree of extracellular hydration also was observed in mice given 0.85% sodium chloride solution; whereas the volume of extracellular fluid was increased, the febrile seizure threshold was unchanged.

It is well known that cellular hydration may enhance the susceptibility to seizures unassociated with fever. McQuarrie[3] showed that excessive hydration would precipitate convulsions in patients with grand mal epilepsies. In a study of the effects of water intoxication on the electroencephalogram of rats, Gellhorn and Ballin[19] have reported the occurrence of slow potentials of large amplitude and spike discharges, sometimes accompanied by overt convulsions. Crawford, Dodge, and Probst[20] have observed similar electroencephalographic changes in rabbits. The slowing of cortical potentials which occurs with hydration also has been observed during hyperthermia;[21,22] it is generally interpreted as a sign of diminished cortical excitability and is difficult to reconcile with the increased sensitivity to convulsions. This apparent discrepancy may be explained by the release of the brain stem reticular system from cortical inhibition and the consequent occurrence of seizures of subcortical origin. Thus, in experimental animals with water intoxication or during hyperthermia, electrodes implanted in the brain stem might reveal greater evidence of seizure activity than surface cortical electrodes.

Sodium balance. Concentration of extracellular sodium was closely correlated with the threshold to febrile seizures in young and adult rats. The correlation also was confirmed in mice; a low febrile seizure threshold was observed with hypoelectrolytemia induced by the injection of glucose, whereas a significant rise in threshold was associated with dehydration and increase in concentration of extracellular electrolyte in mice deprived of water.

The relation of hyponatremia to an increase in susceptibility to febrile seizures in animals is consistent with clinical observations. Of 17 children in whom the concentrations of serum electrolytes were estimated within one or two hours of a febrile seizure, 4 (24%) had hyponatremia of 130 mEq. per liter or lower; the levels were 131 to 138 mEq. per liter in the remainder.[23] In these patients, the cause of

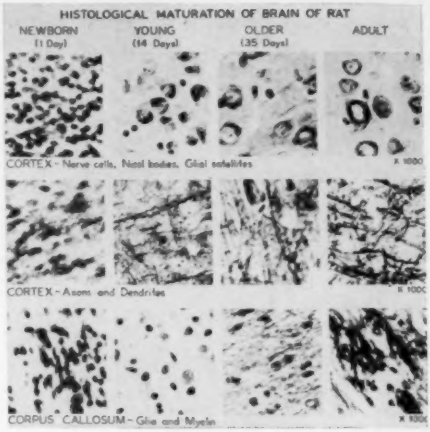

Fig. 5. Photomicrographs of sections of the brain of rats at 4 different ages to show changes in the histology during postnatal development. Cresyl violet and silver stains. × 1,000

the hyponatremia was not determined, but, in 1 case report,[24] a recurrence of febrile seizures was related to administration of tap water enemas and overhydration. On admission to hospital, the patient was febrile, deeply comatose, and convulsing intermittently; the serum sodium concentration was 106 mEq. per liter. Twelve hours later, after a profuse output of dilute urine, the sodium had risen to 132 mEq. per liter, the patient was more responsive, and the seizures were more easily controlled. The association of hyponatremia and seizures has been reported in children with acute infections of the central nervous system;[25] the low serum sodium concentrations appeared to be due to an acute expansion of the extracellular fluid volume. Limitation of intake of water was recommended for prevention of these seizures and administration of hypertonic sodium chloride solution for their control.

During acute infections that do not involve the nervous system directly, such as those sometimes associated with febrile seizures, an expansion of the plasma volume has been observed as the result of the fever per se.[26] Thus, administration of water or hypotonic fluids in excessive amounts during the acute

stage of a febrile episode would seem irrational and, indeed, potentially dangerous in patients susceptible to seizures.

Modification of the febrile seizure threshold by anticonvulsant drugs is of interest in relation to the associated changes in the balance of water and electrolytes in the brain.[27] The febrile seizure threshold was elevated by acetazoleamide and lowered by diphenylhydantoin; acetazoleamide tends to stablize the cell membrane and to decrease the rate of influx of sodium into brain cells, whereas diphenylhydantoin causes an increase in the rate of transport of sodium.[13] The exacerbation of the febrile seizure in mice treated with diphenylhydantoin might be explained by an enhanced permeability of brain cell membranes to sodium. The results of these studies are in agreement with clinical observations; diphenylhydantoin, in daily doses of 10 mg. per kilogram of body weight, failed to prevent the recurrence of febrile seizures in all of 7 patients treated.[28]

Potassium balance. The threshold to febrile seizures showed a closer correlation with the concentration and distribution of potassium in the brain than that reported for electroshock seizures.[4] The known effects of acetazoleamide and diphenylhydantoin on the balance of potassium confirm the correlation observed in the present study. Acetazoleamide, which was found to raise the threshold convulsive temperature, increases cellular and the ratio of cellular to extracellular potassium in the brain.[13,14] Diphenylhydantoin, which failed to raise the threshold temperature, does not modify the concentration of cellular potassium.[13]

Brain histology and chemical analyses. The postnatal histologic changes in the brain of the albino rat have been described in detail by Sugita.[29] He illustrated in drawings the immaturity of the cortex at birth compared with its complete organization by the twentieth day. Indeed, all the major areas of the adult cortex are present at 10 days of age. From the tenth to the twentieth day after birth, few new cells make their appearance and this phase is characterized by cellular enlargement and the development of axons. Myelinization, which begins in the latter half of this phase, is complete at the ninetieth day.

By means of the photomicrographs of equal magnification shown in Figure 5, directional changes in the estimated volume of the cellular and extracellular spaces in the brain during development may be compared with the histologic maturation. For example, the relatively greater volume of intracellular water in the brain of older and adult rats compared with the newborn appears to be related to the increase in size of the neurons and development of axons, dendrites, and glial cells; the differences observed in the balance of water and electrolytes in the brain of adult compared with 1-month-old rats may be related to the degree of myelinization and the selective affinity of lipids for electrolytes.[30] However, in the newborn, the permeability of cell membranes to the chloride ion may be increased and this factor may explain in part the lack of conformity of the analyses of electrolytes at this age.

Though it is generally recognized that the chloride space is not identical with the extracellular space, several investigators have concluded that changes in the volume of the cellular and extracellular spaces occur in parallel.[4,31] In the present investigation, the chloride space has been employed as an index for the estimation of directional changes in the volume of extracellular fluid. With this assumption, the results of the study indicate that the concentration and distribution of electrolytes in the brain may explain in part the heightened susceptibility to febrile seizures in young compared with adult animals.

APPLICATION OF LABORATORY STUDIES TO FEBRILE SEIZURES IN CHILDREN

The evaluation of factors concerned in the mechanism of febrile seizures in animals may in part be reconciled with clinical observations. The susceptibility to febrile seizures is related to age and is greatest in infants and young children; the threshold convulsive temperature in some infants approximates that of newborn rats.[1] In less susceptible children, it is possible that the degree of fever necessary for induction of seizures would be higher than that attained clinically with infection and comparable to the convulsive temperature observed in older animals. The disparity between the average convulsive temperature observed in

children and in animals may possibly be explained by differences in degree of maturation or by a lowered threshold to febrile seizures, which, in a high percentage of children, appears to be inherited.

That the degree of fever required to induce seizures in young animals may have an effect qualitatively similar to that which occurs in children is suggested by a low rate of mortality of the test animals and the lack of destruction of carbonic anhydrase, an enzyme intimately involved in the metabolism of electrolytes.[7] Furthermore, the results of clinical studies have tended to confirm the laboratory data. The threshold to febrile seizures was dependent upon the height of the body temperature in both children and in animals.[1] The threshold was lowered in states of overhydration and hyponatremia, and the seizure was not controlled by treatment with diphenylhydantoin.

These confirmatory clinical reports attest to the value of evidence obtained in animal experiments and its application to subsequent clinical studies. Though the final evaluation of additional factors involved in the mechanism of febrile seizures and of potential therapeutic agents must be made clinically, the laboratory results presented should facilitate the design of clinical studies and unnecessary and sometimes hazardous procedures in patients may be avoided.

The author is indebted to Dr. Gino Di Virglio of the Department of Anatomy for the histologic sections and photomicrographs and to Mr. Patricio Hernandez for his valuable technical assistance.

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Henry Wise Newman

(1907 - 1959)

"As a teacher of the neurologic disciplines, he was without peer . . ."

Dr. Henry Wise Newman, professor of medicine (neurology) at Stanford University School of Medicine, was born in Fresno, California, on April 6, 1907, and died in Belvedere, California, on September 19, 1959. He received his A.B. degree from Stanford in 1927 and his M.D. degree in 1931. He began his postgraduate training as a resident in neuropsychiatry at the Stanford University Hospitals, San Francisco, in 1931. During 1937-38, he served as a Rockefeller Fellow at the National Hospital, Queen Square, London. In 1956, Dr. Newman became professor of medicine (neurology) and chief of the Division of Neurology.

Dr. Newman engaged in research that encompassed nearly every aspect of neurology and clinical neurophysiology, with main emphasis on studies of the metabolism, pharmacology, and physiology of alcohol; his monograph, *Acute Alcoholic Intoxication*, was published in 1941. From 1942 to 1946, he served in the Medical Corps, United States Navy, and attained the rank of lieutenant commander. He also served as neurophysiologist at the U. S. Naval Hospital, Oakland, California, in the investigation of war injuries to nerves. In 1951, he was appointed to the World Health Organization Expert Advisory Panel on Drugs Liable to Produce Addiction. In addition to the research activities that led to the publication of nearly 100 significant papers and a revision of the 1941 edition of his monograph, Dr. Newman continued his role as a clinician and teacher. As a teacher of the neurologic disciplines, he was without peer, not because of expansiveness, dogmatism, or a tendency to oversimplify but rather because of his ability to humble himself before some of the yet insoluble problems of illness and his willingness to point out that man cannot understand all the ways of nature. If Henry Newman did not know, he said so, but no one ever felt that such a statement was easy for him. When he dealt with a problem, be it clinical or in the laboratory, no portion of it remained unprobed. This same attitude was directed to his patients, leaving him with an intensely loyal following.

WILLIAM W. HOFMANN, M.D.

CASE REPORT

Bilateral acoustic neurinomas with multiple meningiomas

B. W. Rovine, M.D., and E.H. Mulford, M.D.

THIS REPORT is presented to document an unusual case of multiple intracranial tumors.

The patient, a 45-year-old Negro female, was admitted to the Norwalk Hospital on July 11, 1955, for study. She complained of bilateral deafness of ten years' duration and diffuse headaches and visual blurring of several months' duration. She was luetic and diabetic. There was no family history of deafness or skin changes. Examination revealed a hard excrescence in the left posterior parietal region of the head, bilateral papilledema and bilateral nerve deafness. Skull x-rays demonstrated a hyperostotic lesion corresponding to the clinically apparent mass. Dr. Russell Miller, radiologist at the Philadelphia General Hospital, interpreted this hyperostosis as consistent with Paget's disease or meningioma.

A biopsy of the mass in the left parietal region was carried out, and the material obtained was strongly suggestive of meningioma. Ventriculography was next performed, together with craniotomy and complete removal of the involved bone in the left parietal area. There was some roughening of the dura underlying the bony lesion but no evidence of any intracranial tumor. This tumor in the bone was proven to be meningioma.

Although technical difficulties were encountered, the ventriculograms suggested bifrontal space-occupying lesions. The cerebrospinal fluid obtained contained 70 mg. per cent of protein and gave negative mastic and Wassermann reactions.

Because of the pneumographic suggestion of frontal masses, a 2-stage right frontal craniotomy was carried out. A 2 x 1.5 x 1 cm. meningioma on the undersurface of the frontal dura was removed. Following this, the transcortical removal of a large meningioma in the right frontal lobe was attempted. This tumor, which had its origin on the falx cerebri, could not be completely removed and was not measured. The falx cerebri was incised and tumor discovered on its left side. Following this operation, the patient remained unconscious; left hemiplegia developed, and she died.

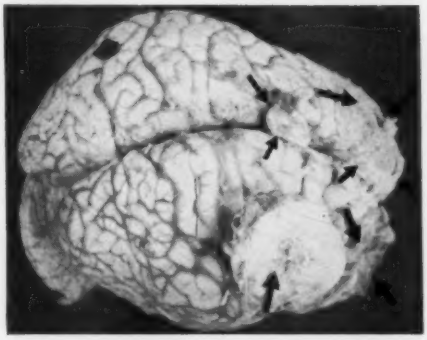

Fig. 1. The arrows point to the meningiomas of the convexity and frontal lobes. The square shows the location of the original extradural meningioma.

At autopsy, the brain was removed and examined. In addition to the 3 tumors already mentioned, 3 more were discovered. A meningioma of the convexity, measuring 5 x 4 x 3 cm., depressed the cortex in the right frontorolandic area. The other 2 were acoustic nerve tumors, the right measuring 2.5 x 2 x 1.5 cm.

From the Norwalk Hospital, Norwalk, Conn.

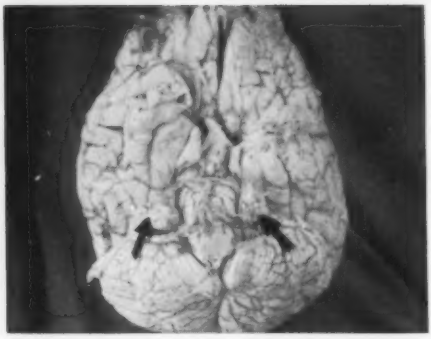

Fig. 2. The base of the brain, showing the bilateral acoustic tumors

and the left, 2 x 1.5 x 1 cm. After hardening, the brain was sectioned and the 2 deep frontal lobe tumors were found to be 1, originating on the falx and infiltrating most of both frontal lobes. All the others were separate and distinct, making a total of 6 tumors. The autopsy disclosed no evidence of neurofibromatosis.

Histologically, the acoustic nerve tumors showed the appearance of typical neurinomas of the neoplastic variety with interlacing groups of fibers, palisading of nuclei, and Verocay bodies. In 1 of the sections, the tumor was seen to have engulfed the geniculate ganglion.

The meningiomas were all meningotheliomatous and psammomatous. The original tumor, which presented as a mass in the skull, was shown to have invaded the bone microscopically.

There is ample incidence in the literature of multiple meningiomas, and reports exist of meningiomas associated with many other types of intracranial tumors.

We have been able to find reports of 5 cases of bilateral acoustic neurinomas associated with single or multiple meningiomas; 2 cases were from Cushing's series of meningiomas as reported by Cushing and Eisenhardt[1] in 1938, and 1 case was presented by Ilsey and Hall[3] in Los Angeles in 1940. The fourth case was reported by Davidoff and Martin[2] in 1955 and, interestingly enough, was the daughter of one of Cushing's patients. The authors reviewed the cases of both daughter and father from the viewpoint of the possible hereditary tendency of their tumors. Another case was reported in the Italian literature in 1955.[4]

Our patient was a Negress. All of the patients in the cases cited above were of Caucasian race. Cushing and Eisenhardt[1] have cited the comparatively low incidence of meningiomas in the Negro.

SUMMARY

We have presented the case of a patient who had a total of 6 intracranial tumors, 4 of which were meningiomas and 2, acoustic neurinomas. This patient had no familial history of deafness or neurofibromatosis. She showed no clinical or autopsy evidence of von Recklinghausen's disease. Her acoustic tumors showed the appearance of the neoplastic rather than the neurofibromatous type. In addition, she was of Negro race.

We believe these facts and findings make this an unusual and interesting case, worthy of being reported herewith.

The authors wish to thank Dr. Helena Riggs for her assistance and advice in preparing this material.

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CASE REPORT

Transverse myelitis with recovery: the only manifestation of systemic lupus erythematosus

Donald P. Granger, M.D.

SINCE THE ADVENT of a reliable diagnostic test for systemic lupus erythematosus, several articles have appeared drawing attention to the protean character of the nervous system signs and symptoms that may occur in that disease. In most of those reports, however, the neurologic signs developed late in the disease or concurrently with widespread systemic manifestations. Isolated spinal cord involvement has been reported in very few cases, and even more rare is recovery after such involvement. For this reason, the following case is reported, in which the only overt symptomatology to date of systemic lupus erythematosus has been monosymptomatic paraplegia, presenting initially a perplexing diagnostic problem and eventuating in complete recovery.

CASE HISTORY

L. S., a 25-year-old Negro female, was admitted to the hospital complaining of weakness in the legs. History revealed an acute illness, beginning ten days earlier, with pricking paresthesias in the left leg, followed in a day by similar symptoms in the right leg and lower back. Within days, a burning sensation appeared girdling the abdomen. Three days after the onset of symptoms, she had been examined by an emergency ward physician at this hospital and no neurologic abnormalities were noted. After this examination, the patient reported development of weakness in the left leg, causing her to limp; this rapidly progressed, so that she was barely able to support her own weight. At the same time, there had been some vague aching in the arms and an episode of urinary incontinence due to extreme urgency.

A mild respiratory infection occurred two weeks before the onset of this illness. The only medical history of significance was an episode of painful paresis of the left arm two years earlier, which had been diagnosed as "bursitis" and improved without residuum. There was no history of recent trauma.

Examination at the time of admission, ten days after onset, revealed a thin young woman who appeared quite ill and in moderate discomfort from weakness of her legs. She had a low grade fever of 99.6° F.; tachycardia, 98 per minute; and normal blood pressure and respirations. General examination was unremarkable; the neck was supple. The principal neurologic findings were weakness and diminished sensation in the lower extremities. Unassisted gait was impossible, but, with help, the patient could walk dragging the left leg behind her. With difficulty, she could stand unaided for brief intervals. Muscle strength was markedly diminished in the left leg, less so on the right. The right arm seemed weaker than the left. No muscle atrophy, asymmetry, or fasciculations were noted. Reflexes were bilaterally equal but present only with reinforcement in the legs. The right plantar response was normally flexor; there was no response on the left. Vibration sense was absent in the right leg below the hip and in the left leg below the knee. Position sense was vaguely present in

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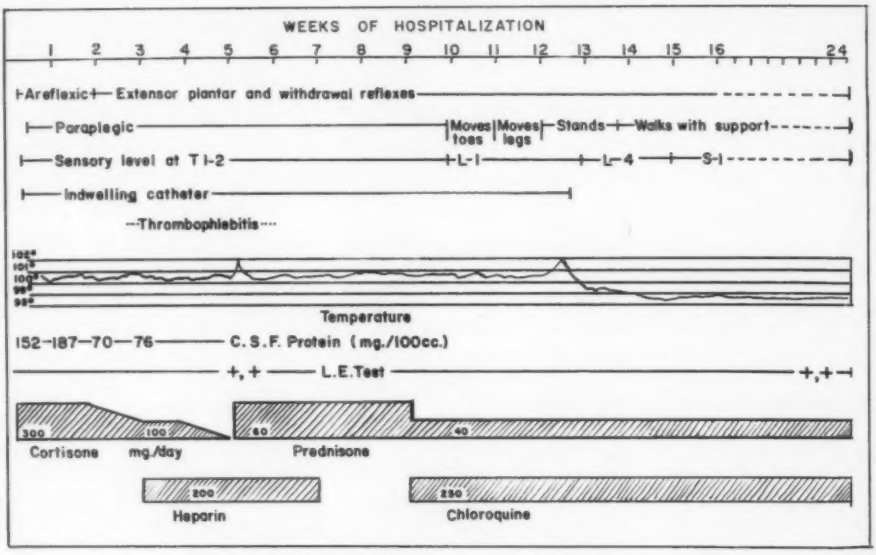

Summary of clinical and treatment data

both legs. Touch was absent on the right below the lower abdomen and on the left below the knee; pain and temperature were diminished on the right below the lower thorax and approximately normal on the left.

Laboratory studies showed normal hemoglobin and white cell counts. The urine showed a +4 albuminuria, occasional red and white blood cells, and 1 to 2 fine granular casts per high powered microscope field. Serologic tests were nonreactive, and the blood sugar, blood urea nitrogen, serum electrolytes, and liver function tests were normal. There was a reversal of the serum proteins with an albumin of 2.3 and globulin of 4.5.

Lumbar puncture showed normal initial pressure and response to the Queckenstedt test. The cerebrospinal fluid contained a protein of 152 mg. per cent, normal sugar, and a few fresh red blood cells considered secondary to the trauma of the tap. A Kolmer test was nonreactive, and the mastic was 5555433110. Electrophoresis of the cerebrospinal fluid showed a gamma globulin of 25.8%, compared with a top normal value of 18%. Viral studies of the stool and spinal fluid were negative for poliomyelitis. X-ray examinations of the chest and cervical spine were within normal limits, as was an electrocardiogram.

The patient had a protracted illness that showed early rapid changes in her neurologic status (see chart). Two days after admission, she became febrile to 100.8° F., and thereafter her temperature fluctuated between normal and 102° F. At this time, she was found to have increased weakness of both legs and a thermal sensory level to T2. An indwelling catheter was required to relieve complete urinary retention. Repeat lumbar puncture at this time showed a protein of 182 mg. per cent without cells. Intravenous ACTH was begun, 20 units over eight hours, and cortisone was given, 300 mg. daily for the first eight days, then tapering to 100 mg. per day. At the end of one hospital week, the patient was totally areflexic, and touch, temperature, and position sense were not perceived below T2. Pain was felt in patchy areas below that level, as was vibration. The leg muscles now showed diminished tone and almost total paralysis; the arms remained strong.

After eighteen days without change, an early extensor plantar response was found on the right, and, within a few days, this became a

more generalized withdrawal reaction. The patient then complained of pain in the legs and clinically was thought to have a thrombophlebitis. Sodium heparin was given for thirty days, and the signs of phlebitis subsided. From the third to the fifth hospital week, the patient's course was stable, with constant fever without leukocytosis, repeated white blood cell counts being below 5,000 per cubic millimeter. In the fourth week, she did complain of severe abdominal pain and by physical and x-ray examinations was considered to have a paralytic ileus. This subsided spontaneously within thirty-six hours. Cystometrogram at this time showed an autonomous bladder. In the fifth hospital week, the first of 2 positive LE tests was obtained. Because of the absence of improvement on cortisone, that drug had gradually been reduced and discontinued. After the results of the LE test were obtained, prednisone was begun and continued for the remainder of the hospitalization in doses varying from 60 to 40 mg. daily.

Two months after admission, chloroquine was begun, a loading dose of 750 mg. being followed by a daily dose of 250 mg.; this was also continued until discharge. One week after this, the patient was able to move her toes slightly, the first change in her condition in six weeks, and complete sensory testing revealed a return of perception of all sensory modalities to the level of L1 bilaterally. Two weeks later, the temperature curve began to show more persistently normal values and repeat cystometrogram showed a reflex neurogenic bladder. The urinary catheter was removed and voiding accomplished by pressure on the abdomen. In another two weeks, the patient was voiding satisfactorily and the sensory deficit remained only below the knees. Greater volitional motion was now possible, and, at this point, intensive physical therapy was begun.

Three and one-half months after admission, at the time of her transfer to a separate rehabilitation hospital, complete examination showed only reduction of light touch sensibility below the ankles, diminished pain sense below the knees, and absent vibration and position sense in the ankles and toes. There were bilateral extensor plantar reflexes. The patient was able to walk with crutches and knee braces, and both bladder and bowels were functioning well. Her temperature had not ranged above 99.4° F. during her final two weeks of hospitalization.

In the rehabilitation center, the patient was continued on chloroquine and prednisone for an additional six weeks, the latter drug being withdrawn gradually and ACTH gel used briefly. Lumbar puncture at that center showed a clear fluid with normal manometrics, a protein of 20 mg. per cent, and mastic of 1111111000. Urine albumin was 0 to +1, and plasma proteins were normal; 2 subsequent LE tests at another hospital were positive. The patient was discharged from the center able to ambulate with the support of a single cane.

Follow-up examination two months later, seven months after onset of illness, found the patient without subjective complaints. She was performing all her normal household functions. She denied any paresthesias and, except for occasional nocturia, had normal bladder and bowel function. Her libido had returned to normal, and appetite and weight were as before illness. General physical examination was normal, and neurologic examination revealed only a slight clumsiness on heel to knee testing; moderate residual weakness in the legs, more so in the distal muscles; absent abdominal reflexes; and a left extensor plantar response. Other tendon reflexes were very hyperactive, and sensory tests were entirely normal. The patient was taking no medication.

DISCUSSION

The course of this patient's illness together with the laboratory findings make quite certain the diagnoses of myelitis and lupus erythermatosus; it is most probable that the former was due to the latter. A few review articles[1–3] reporting large series of patients with SLE have now appeared, noting the neurologic signs that may be present in patients with this disease and the possibility of their occurrence as a primary symptom. However, from a review of the literature, nervous system involvement as the only clinical feature of the disease would appear to be a rarity. Usually, the diagnosis of neurologic involvement in SLE has either been retrospective or occasioned by the already florid picture of the generalized disease. In this case, as in the well studied patient reported by Scheinberg,[4] there

were no early findings of a clinical or laboratory nature which could not be explained by the severity of the neurologic problem. Steroid therapy, used almost from the onset of the disease in an effort to abort total paralysis, may have masked further findings, but it is of interest that the clinical picture did worsen during their use and the various laboratory reflections of physiologic aberration did not improve.

Few cases of neuritis and myelitis without either systemic or more total neurologic involvement have been reported, and the latter syndrome as an isolated finding in SLE must be unusual. A case reported by Sedgwick and Von Hagen[5] had a mononeuritis with cytoalbuminologic dissociation, but, as Scheinberg has noted, in the absence of reflex changes or pathologic proof of widespread collagen disease, this diagnosis may be questioned. Siekert and Clark[6] reported a series of patients with early neurologic signs and lupus, and their second case had a myelitis the history of which somewhat resembles this case; however, the diagnosis was entertained only retrospectively, after a more generalized picture of lupus had occurred. In the large series recently reported by Armas-Cruz and associates,[3] with 36 of 108 cases of SLE showing nervous system involvement, there is mention of only 1 case of flaccid paraplegia, showing some improvement after a year of cortisone therapy. Similarly, in the 100 cases reported by Clark and Bailey,[2] 1 of the 24 patients with neurologic signs is said to have had a paraplegia. The 2 cases with cord involvement in the group reported by Bailey, Sayre, and Clark[7] had a cytoalbuminologic dissociation similar to our patient; this is true also of Scheinberg's case, suggesting this as a constant feature of the condition. In these 3 cases mentioned, despite the use of steroids, there was a fatal outcome, emphasizing the unusual nature of the recovery in the case reported here.

Whether this recovery can be attributed to the use of chloroquine is certainly problematic. In the review of SLE by Dubois[8] in 1956, 38.6% of 163 cases of the generalized form of the disease were noted to undergo spontaneous remission, indicating the hazards of ascribing improvement in any single case to any single drug. However, Dubois also mentions improvement in 80% of milder cases with the use of antimalarial drugs, and, in a recent article by Tye and associates[9] evaluating combined therapy in lupus, both discoid and systemic, 2 of 3 cases of the subacute form of the generalized disease were said to be improved. In our patient, there was essentially no change in the clinical or laboratory picture with prolonged steroid usage, but, shortly after the institution of chloroquine therapy, dramatic improvement ensued. It should also be noted, however, that some cases of transverse myelitis, from any cause, will undergo spontaneous and complete recovery. So the problem of judging a drug's action in a case such as this is made much more complex.

One can only speculate on the nature of the lesion in this patient, causing such total and prolonged interruption of function but permitting essentially complete recovery. In the 2 cases already mentioned reported by Bailey and associates, there was extensive degeneration and demyelination of the dorsal columns and posterior root ganglia. However, that the cause for our patient's symptoms was primarily vascular is supported by the perivascular demyelination found by Piper[10] in a case of hemiplegia and the 3 cases with encephalomalacia due to endarteritis reported by Glaser.[1] Heptinstall and Sowry[11] also reported a case in which there had been weakness and absent deep tendon reflexes in addition to cerebral symptoms; they found ischemic changes which they thought due to an obliterative arteritis. Finally, Case 31 reported by Hill[12] also showed a polyarteritis in both the spinal cord and peripheral nerves.

As mentioned before, cases of isolated nervous system involvement in SLE have thus far been rarely noted, but this will undoubtedly change with the current accuracy of laboratory diagnosis. One such case, pointing out the diverse findings that may be encountered in the disease, is in the series of cases of unilateral internuclear ophthalmoplegia reported by Cogan, Kubik, and Smith;[13] in the 1 case of 8 in which pathologic examination was possible, lesions typical of lupus were found. Similar cases surely have gone undetected in the past, but, with the LE tests now available, the diagnosis must be considered in otherwise unexplained neurologic disease.

SUMMARY

A case is described in which the presenting symptoms of a peripheral neuritis rapidly progressing to a syndrome of myelitis with total loss of function were found due to systemic lupus erythematosus. This occurred in a young woman who had suffered no other symptoms of that disease. Steroids did not alter the clinical course of the disease, but rapid and functionally total recovery followed the use of chloroquine. The unusual nature of isolated myelitis in SLE has been discussed and the singular recovery in this patient contrasted with the few other cases in the literature. The suspicion of SLE in bizarre neurologic syndromes is again stressed, along with the suggestion of a possible efficacious result from the use of antimalarial drugs.

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Neurology

BOOK REVIEWS

The History and Philosophy of Knowledge of the Brain and its Functions

edited by F. N. L. Poynter, 277 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $5.50

This is an account of a symposium sponsored by the Wellcome Historical Medical Library with the cooperation of the National Hospital, Queens Square, and the Institute of Psychiatry, University of London. Since many of the topics are unusual and some esoteric, they are presented here in detail.

Wilder Penfield presided at the first session and discussed, as a Hippocratic preamble, the brain and intelligence. This was followed by a historical review, concepts of the brain and its functions in classical antiquity, by D. H. M. Woollam and by discussions of body and soul in Aristotelian tradition by J. S. Wilkie and of non-Western concepts of psychic function by I. Veith.

Under the chairmanship of Pearce Bailey, M. Critchley presented a paper on the origins of language; D. Williams, one on old and new concepts of the basis of consciousness; and R. Brain, on Hughlings Jackson's ideas of consciousness in the light of today.

J. C. Eccles presided at the third session, during which W. Pagel described medieval and Renaissance contributions to knowledge of the brain and its functions; W. Tiese, Descartes' ideas of brain functions; and W. P. D. Wightman, wars of ideas in neurologic science from Willis to Bichat and from Locke to Condillac.

Bernard Hart was chairman of the fourth session, at which E. H. Ackerknecht presented the contributions of Gall and the phrenologists to knowledge of brain function; G. W. Harris, emotions and the pituitary in the nineteenth century; and H. McIlwain, chemical contributions, especially from the nineteenth century, to knowledge of the brain and its functioning.

In the final session, under the chairmanship of W. Le Gros Clark, Mary Brazier discussed the evolution of concepts relating to the electrical activity of the nervous system, 1600 to 1800; F. Walshe, some reflections upon the opening phase of physiology of the cerebral cortex, 1850-1900; and, finally, C. Brooks, current developments in thought and the past evolution of ideas concerning integrative function.

This is a volume rich with the history and lore of neurology, inviting the reader at every turn to pursue the fascinating bypaths of his field.

A.R.V.

Handbook of Physiology: Section 1, Neurophysiology

Editor-in-chief, John Field, section editor, H. W. Magoun, 779 pp., Williams & Wilkins, Baltimore, 1959. $22

Brought out by the American Physiology Society, the *Handbook of Physiology,* of which this is Section 1, Volume 1, was "designed as

a repository for the body of present physiological knowledge systematically organized and presented." The current section is the first of 3 designed to present the subject matter of neurophysiology. It commences with 8 introductory chapters and proceeds through 22 other chapters covering a diversity of topics. Each is the work of an authority. The work is so outstanding that it is next to impossible to select single chapters for mention. However, the historical development of neurophysiology by M. A. B. Brazier will have universal interest, and chapters by H. Gastaut (The physiopathology of epileptic seizure) and W. H. Sweet (Pain) will be important for the clinical reader. The whole makes up the first section of an outstanding reference work in an important aid of basic neurology. The format is excellent, and the illustrations are superb. A must for those who would collect the memorabilia of neurology.

A.B.C.

Regulation of Cell Metabolism

edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, 387 pp., ill., Little, Brown & Co., Boston, 1959. $9.50

This recent addition to the growing list of Ciba Foundation Symposia volumes records the presentations and discussions at a Symposium held in July 1958 under the chairmanship of Sir Hans Krebs. The subject is of fundamental importance to biochemistry and physiology and, in keeping with its importance, commanded a most distinguished group of participants. The Symposium opened with an excellent statement by Krebs, introducing the 6 main papers on intracellular structure and its relations to metabolic regulation (Siekevitz and de Duve); control of oxygen utilization (Slater and Chance); sites of control of oxidative phosphorylation (Lehninger); and alternate oxidative pathways (Dickens). These were followed by "Short Communications" covering 2 main subjects: glycolysis, fermentation, and the Pasteur effect (Racker, Potter, Lynen, and Holzer) and growth and control of enzyme synthesis and activity in bacteria (Pardee, Dean and Hinshelwood, and Magasanik) plus a paper on glycogen synthesis (Lipmann) and one on alternate pathways of electron transport (Martius). In addition to the formal presentations, the extensive discussions contain much of interest. For example, Chance described attempts to utilize digital computer analysis of interactions of glycolysis and respiratory metabolism (pp. 219-226), and there is an extensive discussion of feedback principles and mechanisms as they may apply to biochemical systems and their regulation (pp. 354-368).

As Krebs pointed out, this is the first book surveying a variety of aspects of nonhormonal regulation of cellular metabolism. The papers and discussions focused on such regulatory factors as intracellular compartmentation, DPN, ADP, inorganic P, DPN-TPN interrelationships, metabolic feedbacks, and enzyme induction or repression. This volume should appeal to a much wider audience than some of the more technical symposia that have appeared in this series. The metabolic systems considered (glucose utilization, oxidative pathways, coupled phosphorylation, and the like) and the fundamental questions of how these processes are controlled and regulated should be of particular interest to neurochemists and other neurologic scientists. Even though there is relatively little direct reference to neural tissue, the volume contains so much that is particularly relevant to neural metabolism and function that it should be required reading for the neurologic scientist as well as biochemists and physiologists in general.

D.B.T.

Biological and Biochemical Bases of Behavior

edited by Harry F. Harlow and Clinton N. Woolsey, 476 pp., ill., University of Wisconsin Press, Madison, 1958. $8

This well-planned, well-edited volume is based on a symposium of the same title. It may be regarded as an authoritative presentation of the present status of our knowledge of the physical substratum of behavior.

The reviewer has before him his copy of C. J. Herrick's book of an analogous title, published in 1924, *Neurological Foundations of Animal Behavior*. Here is the base erected by the great American comparative neurologists which affords the firm foundation of the present day research. Herrick, who is still

with us at well past the age of 90, perusing the present volume, cannot but feel pleased with the impressive progress made in the understanding of the physical factors in behavior during the past thirty-five years.

Contributors to the present volume, each of whom present topics in their field of established competence, are H. F. Harlow, J. C. Lilly, W. D. Neff, I. T. Diamond, J. E. Rose, K. H. Pribram, D. R. Meyer, J. V. Brady, J. Olds, F. A. Beach, D. B. Tower, M. R. Rosenzweig, D. Krech, E. L. Bennett, R. W. Sperry, A. H. Riesen, and D. O. Hebb.

The book is an important link in bringing together and unifying the data presented by psychology with that presented by anatomy, physiology, and chemistry. One would wish that this volume would have a wide circulation to the end that it would serve as another *rapprochement* between the psychologic and physical sciences.

A.R.V.

Anastomoses Between the Leptomeningeal Arteries of the Brain

by Henri M. vander Eecken, preface by Raymond D. Adams, 160 pp., ill., Charles C Thomas Co., Springfield, Ill., 1959.

The notion of "terminal arteries" in the brain (Cohnheim) is a remarkable example of how a brilliant misconception compounded with a widespread misunderstanding stimulated for more than three-quarters of a century the extraordinary amount of controversy, research, and more controversy which, leaving the main issue unresolved, yielded a huge body of capital information on the vascular anatomy and circulation in the brain.

This monograph gives a definitive answer to the main point at issue in the problem of the anatomic substrata and mechanism of the collateral blood supply after occlusion of one or another of the main arteries of the brain and of cerebellar arteries. The evidence presented seems to clarify the misunderstanding. Vander Eecken's argument is a logical consummation of the prolific ideas of the late Charles Foix, who thirty-five years ago with Hillemand provided lucid terms of reference for the arterial vascularization of the forebrain and who with Gabrielle Levy stated the law of the gradient in the ischemic softening from the constant and complete proximal to the occlusion to a variable and incomplete distal from the occlusion.

Vander Eecken marshals his evidence from the macroanatomic study of 40 adult cerebrums with a personal method of selective arterial injections; from a study of the development of the arterial vascularization of the brain in 30 fetal cerebrums from eleven weeks of gestation to one and a half months after birth; from a comparative anatomic study of cerebral vascularization in lissencephalic and gyrencephalic mammals; and from clinicopathologic experience with cerebrovascular occlusions at the Mallory Institute of Pathology and Massachusetts General Hospital in Boston and at the Department of Pathology of the University of Ghent in his native country. His findings and conclusions are explicit. The capillary bed is universal and common to all branches of the cerebrovascular tree. However, in the case of an arterial occlusion, this huge vascular bed does not in itself represent an adequate means of supplemental collateral blood supply. The perforating arteries of the base of the brain, which in Foix's and Hillemand's scheme would correspond to the system of the short circumferentials for the telencephalon (Y.), have only exceptionally anastomoses between them. They are nearest to being "terminal" in Cohnheim's sense, and so the deep cerebral infarcts in the internal capsule, basal ganglia, and thalamus are usually massive, sharply circumscribed, and relatively constant from one individual to another in the topography of their distribution.

On the other hand, the leptomeningeal arteries, which in Foix's and Hillemand's classic scheme would correspond to the long circumferentials of the end brain and which perforate the pia and irrigate the cortical plate and the subjacent white matter of the cerebral hemispheres, have abundant anastomoses interconnecting the 3 main arterial branches of the cerebrovascular tree. These anastomoses are found not at random on the surface of the brain but occur in the clearly definable, albeit variable in width, border zones between the zones of anatomic distribution of the middle, anterior, and posterior cerebral arteries. Similar anastomoses also are found between the

3 long circumferential arteries of the cerebellar hemispheres. In a simplified diagram, the disposition of these arterial anastomoses upon the convexity of the hemispheres corresponds to the frontooccipitotemporal curvature of the hemisphere in the sagittal plane (Y.).

To this reviewer, the apparent disregard of the anatomic midline of the end brain by the system of the anterior cerebral artery, which can be double or be a single median vessel, and the abundance of interhemispheric anastomoses is a particularly noteworthy finding. These anastomoses are of 2 types, the "end-to-end" anastomoses and the anastomoses through collateral branches of the end artery, the latter resolving itself directly in a system of precapillary and capillary vesicular net. In his picturesque designation of this latter type of anastomosis, vander Eecken calls it a "candelabra" type of anastomosis. These 2 kinds of anastomoses between the distal branches of main cerebral arteries provide in the case of occlusion of one or the other primary system of blood supply a competent bed of supplemental circulation and explain the great individual variability of the extent, severity, and topographic distribution of the area of ischemic breakdown of cerebral tissue distal to the site of the infarct, whereas proximal to the arterial occlusion the ischemic necrosis is always complete and topographically constant. Such, in essence, is the core of vander Eecken's well documented argument.

The ontogenetic development of the vascular tree of the brain explains the origin of the arterial anastomoses. During the first two embryonal months, there is no subarachnoid space and the vascular bed consists of richly anastomotic, mesenchymal sinusoid channels that permeate the brain wall; at this time, there are as yet no definitive arteries and veins. By the fourth month, the sinusoids differentiate into 2 sets of channels: the superficial set, which become veins, and a deeper set of arteries, which eventually connect with the cephalic branches of the dorsal aortas and form the terminal loop of the circle of Willis. The sinusoids, with a relatively sluggish blood flow, eventually atrophy and are resolved. The sinusoids subject to the greater hydraulic pressure of the circulating blood develop into the arteries of the brain.

Up to about the seventh month of gestation, the long circumferential branches of these arteries form a wicker basket, as it were, of fan-like radial loops that arch over the convexities of the frontal, parietal, occipital, and temporal lobes and connect over the superomedial border of the hemisphere the watershed zones of the middle cerbral artery with those of the anterior and posterior cerebral arteries. In the distal branches radiating from the trunks of main arteries at sharp angle, the hydraulic pressure is greater than 1/2 the proximal branches radiating at nearly a right angle from the main trunks. Thus, the convex (distal) parts of the hemispheres (cerebral cortex) which are in the process of most active growth and differentiation are favored with the greatest pressure of blood supply through the distal branches.

The arterial trunks, which at first lie on the originally smooth surface of the fetal brain, eventually sink into the sulci, while their fanwise sprouting branches supply the now actively burgeoning gyri. This is a brilliant hypothesis. The comparative anatomic study of the leptomeningeal arteries in the lissencephalic and gyrencephalic mammals provides an elegant, albeit inferential, confirmation of the validity of this interpretation of the ontogenetic events in the human brain. The distal anastomotic branches in the border zones between the 3 main arterial systems are maintained by the preferential hydraulic pressure of the blood flow in these zones while the proximal anastomoses atrophy.

Vander Eecken concludes the monograph on a now rationally justifiable optimistic note. These persistent and, in their circulatory competence, important anastomotic channels "may be a factor in limiting the extent of softening in the cortico-subcortical region of the cerebrum and the cerebellum. Systemic blood pressure and physiologic factors play an active part in the correction of regional ischemia and probably influence the circulation through these channels. The problem facing the clinician is how to assist Nature in marshalling these factors in order to restrict the ischemia." This compact monograph contributes to the neurologic literature an excellent piece of well conceived and presented research work.

P.I.Y.

Neurological and Psychological Deficits of Asphyxia Neonatorum

edited by William F. Windle, E. H. Hinman, and Pearce Bailey, 330 pp., ill., Charles C Thomas, Springfield, Ill., 1958.

In significant contrast to great strides made during the last few decades in reducing the maternal mortality in childbearing, the perinatal mortality and crippling of infants show no comparable decrease. Oxygen deficit is a universal risk and an ultimate factor depressing biologic growth and development in man and animals. In mammals, the elemental crisis of birth is the primal and universal risk of life. Of every 1,000 newborn in the United States, 4 develop manifestations of some congenital encephalopathy (cerebral palsy) of one or other type; 3% of the entire population of the United States have an intelligence quotient below 70% and are incapable of a free and independent existence in their natural environment.

This symposium on asphyxia neonatorum represents, in a sense, the opening shot of a program of research mounted on a broad front by the National Institute of Neurological Diseases and Blindness against the factors and causes of perinatal mortality and crippling. The papers were presented at round-table conferences on general biology, physiology, and pathogenic role of anoxia in man and animals and on the organization and management of primate colonies.

In a space allotted for a review, it is difficult to render justice to all contributions to this symposium. Interrelationship of asphyxia at birth, cerebral palsy, and mental retardation is discussed in a well documented review of the present status of the problem by C. L. Bailey. William Windle, the veteran investigator of the role of asphyxia in cerebral damage during development, discusses experimentally produced asphyxia in rabbits. A chapter on learning ability after asphyxiation in guinea pigs is contributed by R. F. Backer. The distortion of patterns of behavior during development in chicks subjected to asphyxiation during incubation is discussed by G. M. Meier. D. E. Reid summarizes this first round-table conference.

Papers on the physiology of asphyxia of newborn by R. E. Cooke, on the factors of survival after asphyxia at birth by J. A. Miller, Jr., on the role of endocrines by C. F. Pfeiffer, and on the relation of anoxia in early gestation to teratogeny by J. Warkany are contributed to the second round-table conference and are summarized b H. E. Himwich. Papers by J. Cammermyer on neuropathology of asphyxia, by G. W. Corner and G. A. Anderson on the effects of fetal circulatory disturbances and asphyxia on the brain of the newborn, by L. G. MacKinley on asphyxia and mental retardation, by M. I. Robert and Ramirez de Arellano on perinatal anoxia and related factors of brain damage in children in Puerto Rico, and by G. L. Brooks on research program in cerebral palsy represent the content of the third round-table conference of special interest to clinicians and neuropathologists.

The 3 papers by J. G. Grontera on the Gayo Santiago Primate Colony, by H. F. Harlow on behavior of infant monkey, and by G. Van Wagenen on breeding and care of monkeys represent the topics of the fourth round-table conference; 34 pages of bibliography and index of subjects complete the book. This volume is valuable as a source of information and of general orientation in an area of research of pressing practical importance.

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1. Brit. M. J., *2*:63, 1957.

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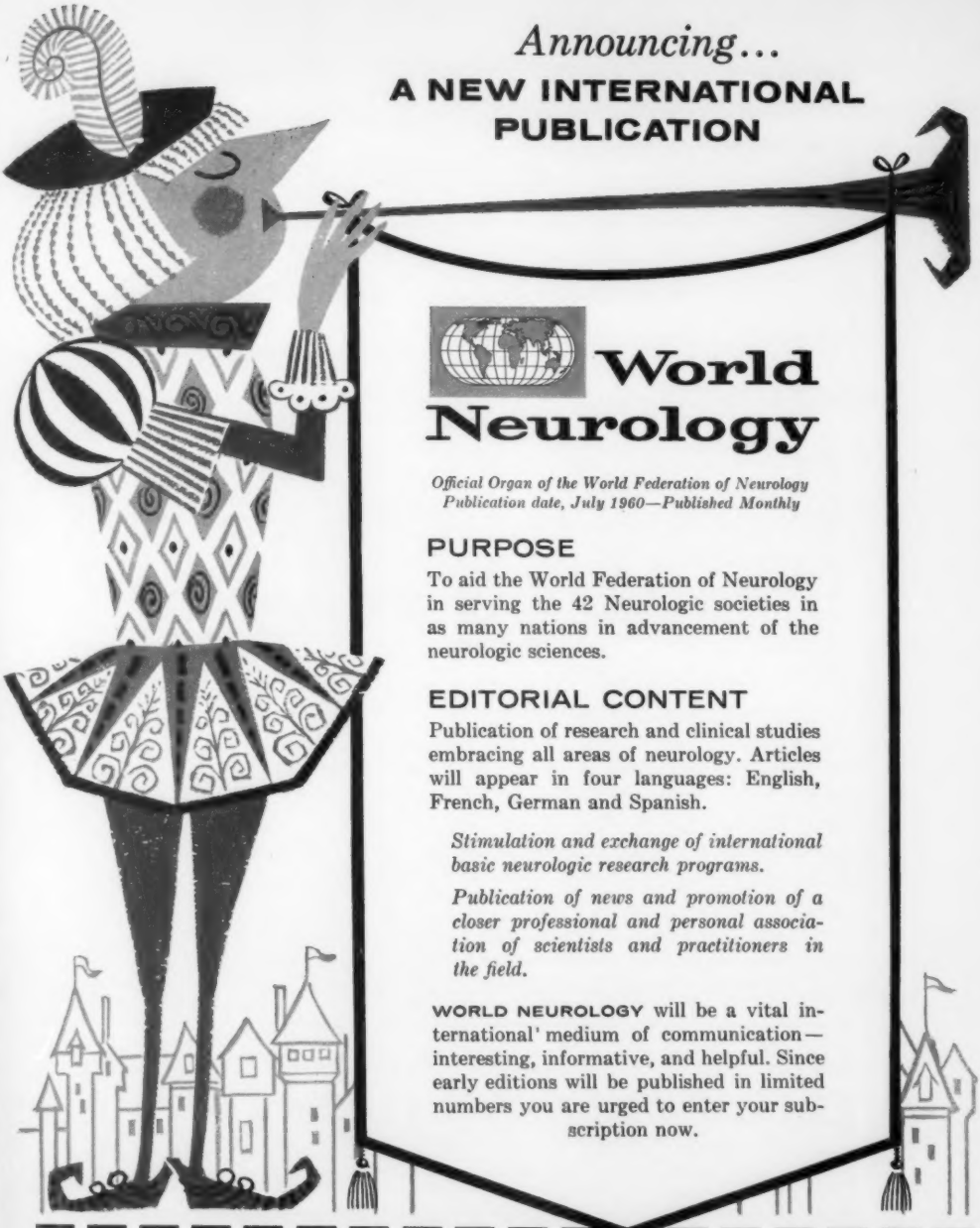

World Neurology

Official Organ of the World Federation of Neurology
Publication date, July 1960—Published Monthly

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To aid the World Federation of Neurology in serving the 42 Neurologic societies in as many nations in advancement of the neurologic sciences.

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:87 (May 2) 1959.

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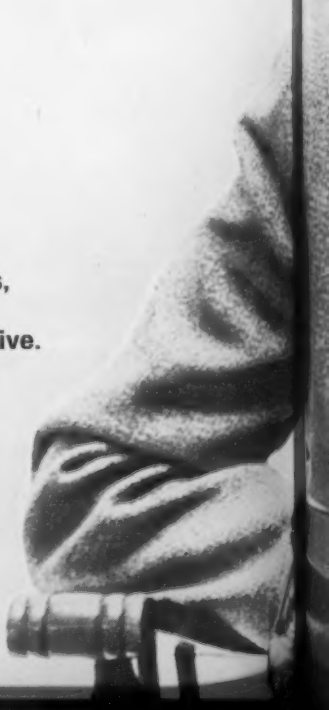

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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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*W.A. Leff, *Antibiotic Med. & Clin. Therapy*. 6: (Suppl. 1), 44-48, Feb. 1959.

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HOW TO USE CATRON: CATRON is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

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DEPRESSION (Endogenous, Reactive, Postpartum, Involutional, and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS: 3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION: Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. Hence, caution should be exercised when combining CATRON with any other drugs such as tranquilizers, phenothiazines, the amphetamines, barbiturates, and hypotensive agents.

HYPOTENSIVE EFFECT—Patients receiving CATRON, but especially elderly and hypertensive patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

VISUAL DISTURBANCES—A reversible red-green color defect has been reported in a few patients, chiefly hypertensives, on extended therapy with CATRON. Discontinue the drug if such changes occur. In a few instances, at unusually high dosage, or where the drug was administered following color disturbances, diminished visual acuity occurred which may be partially irreversible.

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals a neurologic syndrome has been observed, characterized by tremors, muscle rigidity and difficulty in locomotion. Animals displaying this visible neurologic syndrome after prolonged **parenteral** administration usually disclosed a neurologic lesion at autopsy. In other animals these visible neurologic symptoms disappeared following cessation of the drug. No lesions were found after oral administration. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Although pharmacologic evidence indicates that CATRON has a selectivity for the brain, it, as well as other monoamine oxidase inhibitors, may cause hepatitis. Because of the possibility of this life-threatening hepatitis, and of other effects discussed above, the following recommendations and precautions should be observed. If necessary, the patient should be hospitalized to expedite adherence to this regimen.

The Following Precautions Are Recommended:

1. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.
2. Perform regular liver function tests.
3. In all instances daily dose should not exceed 12 mg.
4. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
5. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
6. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked, "Not refillable."

SUPPLIED: CATRON is the original brand of pheniprazine hydrochloride. It is supplied in tablets of 3 mg. and 6 mg., bottles of 50.

BIBLIOGRAPHY: (1) Agin, H. V.: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (2) Bercel, N. A.: Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, p. 331. (3) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, ibid. (4) Kinross-Wright, J.: Experience with JB-516 (CATRON) and Other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (5) Horita, A., and Parker, R. G.: Comparison of Monoamine Oxidase Inhibitory Effects of Iproniazid and Its Phenyl Congener, Proc. Soc. Exper. Biol. & Med. 99:617, 1958. (6) Horita, A.: Beta-Phenylisopropylhydrazine: A Monoamine Oxidase Inhibitor, Fed. Proc. 17:379, 1958. (7) Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, p. 271. (8) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. 3:542, 1959. (9) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

MARCH 1960

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A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

Highlights of AAN Miami Meeting

Program Committee Chairman Joseph M. Foley and Chairman of Local Arrangements Peritz Scheinberg have announced readiness for the Twelfth Annual Meeting of the American Academy of Neurology to be held in the elegant Eden Roc Hotel of Miami Beach (April 25-30). During the general scientific sessions to be conducted Thursday, April 28, Friday, April 29, and Saturday morning, April 30, 39 papers will be presented. Papers on child neurology will be presented as part of the general scientific sessions on Friday afternoon. In addition, the section on neuroanatomic sciences and the section on neurochemistry will conduct a scientific session Thursday afternoon. On Friday morning, the section on neuroanatomic sciences will hold a symposium on the "Pathology of Brain Tumors" and the sections on neurochemistry and neuropharmacology will combine in a symposium on "Frontiers in Neurochemistry." Full abstracts of papers are in the printed program. Dr. James Bull of London will give the Wartenberg Lecture. His subject is "The Volume of the Cerebral Ventricles." The S. Weir Mitchell Prize Award Essay will be presented at 1:30 P.M. Friday as part of the general scientific sessions.... The AAN program will be followed by an Academy-sponsored international conference on vascular disease of the brain which has been organized by a committee headed by A. L. Sahs.

"Laissez Faire" Atmosphere To Dominate Miami Social Activities

While careful plans have been made for scheduled AAN recreation and entertainment in Miami Beach, the major objective has been not to plan too heavily for these functions with the hope that members, their wives, and guests might find in Miami Beach an opportunity to relax and enjoy themselves without a sense of compulsion. The traditional early bird cocktail party will be held Wednesday evening, April 27, in a carefully selected outdoor setting, weather permitting. The annual Academy cocktail party and banquet is booked for Friday night, April 30. For this occasion, some mildly sophisticated entertainment will be added to the conventional speeches. Arrangements have been made for tours and sightseeing trips to neighboring tropical paradises. Mrs. A. L. Sahs, the National Auxilliary Chairman, has worked long and hard with the local committee to arrange for several planned social functions for the women. How-

ever, to use the words of Peritz Scheinberg, the local committee chairman: "I have a feeling that most of the social activities will be conducted on an individual basis by individuals seeking their own entertainment in the many attractions afforded by Miami Beach."

13 New Diplomates Certified in Neurology The American Board of Psychiatry and Neurology certified 13 candidates in neurology at the annual examinations held in New York City December 14 and 15, 1959. Successful candidates are Paul J. Anderson, New York City; Kevin Delgado Barron, New York; Patrick F. Bray, New York; Miriam Willena Carmichael, New York; Archie R. Foley, New York; Gunter Roland Haase, Bethesda, Md.; Elizabeth Jones, Ann Arbor; Robert Katzman, New York; Donald W. Klass, Rochester, Minn.; Elliott L. Mancall, Philadelphia; James D. Ripepi, Philadelphia; David W. Sinton, Albany; and Robert Werman, New York.... All inquiries regarding Board examinations should be addressed to David A. Boyd, Jr., M.D., Executive Secretary-Treasurer, American Board of Psychiatry and Neurology, Inc., 102-110 Second Avenue, S.W., Rochester, Minn.

ANA to Meet in Boston The eighty-fifth annual meeting of the American Neurological Association will be held in Boston's Statler Hotel, June 13 to 15. The scientific sessions will be held on the morning and afternoon of Monday, June 13, and Tuesday, June 14; there will be a morning session only Wednesday, June 15. The annual dinner will be held Tuesday evening. Members wishing a place on the program should submit to the Secretary before March 15 a program abstract not exceeding 200 words and an abstract not exceeding 1,000 words for publication in the transactions. No illustrations will be included in the published transactions. All accepted papers must be submitted to the Editor, Dr. Harold G. Wolff, The New York Hospital, 525 E. 68th Street, New York 21, for acceptance or rejection by the Editorial Board of the Archives of Neurology, now the official journal of the American Neurological Association. The ANA Secretary urges members of the Association to make use of the unique facilities of the Hotel Statler for the display of scientific exhibits and demonstrations. Detailed program regulations for members and invited nonmembers may be obtained by writing to Dr. Melvin D. Yahr, Secretary, American Neurological Association, Neurological Institute, 710 W. 168th Street, New York 32, N. Y.

Cerebral Palsy Group Elects New Officers The American Academy for Cerebral Palsy newly elected officers are Raymond R. Rembolt, Iowa City, President; George N. Eggers, Galveston, President-Elect; Herman Josephy, Chicago, Vice President; Joseph D. Russ, New Orleans, Secretary; and Samuel B. Thompson, Little Rock, Treasurer....The 1960 annual meeting will be held in Pittsburgh on October 5-8 at the Penn Sheraton Hotel.

Chairman of the Program and Publications Committee for this meeting is Randolph Batson, Vanderbilt University, Nashville 5, Tenn.

Joint EEG Certification Committee Established President Augustus S. Rose has announced that a joint AAN-ANA Committee for the certification of electroencephalographers has been formed. The chairman of this new Committee is Robert Aird and the members representing the AAN are Knox Finley, Robert Dow, and Dave Daly. Representing the ANA are Sidney Carter, Ephraim Roseman, and Gilbert Glaser. Reports of this Committee will be circulated to the AAN through the Board of Trustees.

Program for Training in Neurologic Disorders The National Institute of Neurological Diseases and Blindness has opened a special traineeship program open to qualified basic scientists and clinicians for advanced study and research training in neurologic and sensory disorders. To qualify, candidates must have an M.D., Ph.D. or equivalent degree and at least three years of post-doctoral training or experience in this field and must be American citizens or have filed a declaration of intent. Stipends are determined individually, ranging from $6,500 to $17,500 a year. The training period is not less than nine months and does not exceed twelve. All awards are subject to renewal up to sixty months. Further information can be obtained from Chief of Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Neurologic Research Program Established in Detroit According to Dr. J. S. Gottlieb, Director of the Lafayette Clinic, a neurologic research division has been established within the framework of that clinic in Detroit. The objectives of the new program are directed primarily toward the studying of convulsive disorders, mental subnormality, and neurologic factors underlying abnormal behavior. A research fellowship in neurology has been created under the program and is available to selected neurologists who have completed a three-year residency training program and wish to obtain clinical research experience before Board certification. Previous experience in electroencephalography is desirable....Inquiries should be directed to Dr. E. Rodin, Lafayette Clinic, 951 E. Lafayette, Detroit 7, Mich.

Continuation Course in Pediatric Neurology Given The University of Minnesota with the support of the Sister Elizabeth Kenny Foundation gave its annual continuation course February 15-19. The subject of this year's course, under the direction of A. B. Baker, Professor and Director of the Division of Neurology, Paul Ellwood, Jr., Clinical Assistant Professor of Pediatrics and Neurology, and John A. Anderson, Professor and Head of the Department of Pediatrics, was "Pediatric Neurology for

Specialists." The orientation of the course was both basic and clinical. Included in the faculty for the course were Gilbert B. Forbes, Rochester, N. Y.; Herbert H. Jasper, Montreal; Peter Kellaway, Houston; Richard L. Masland, Bethesda; R. M. Norman, Bristol, England; Carl M. Pearson, Los Angeles; L. Rubinstein, London; and Stanley W. Wright, Los Angeles....The traditional J. B. Johnston Lecture was given in Mayo Memorial Auditorium by Herbert H. Jasper, February 18. His subject was "Petit Mal Epilepsy."

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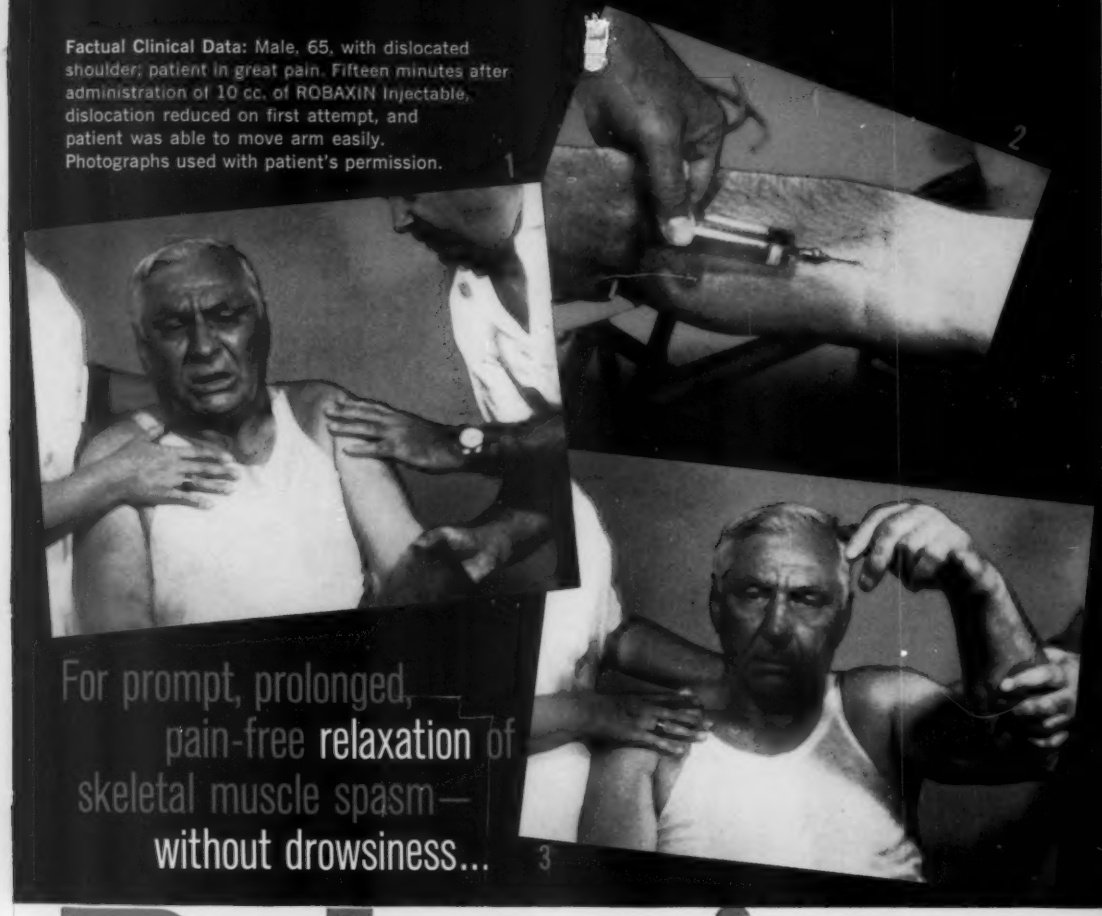

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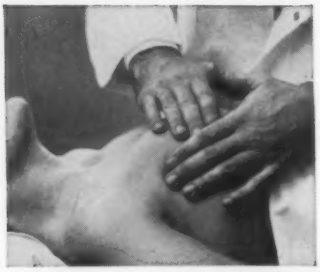

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Sherman Laboratories
Detroit 11, Michigan

1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*–400 mg. *unmarked,* coated tablets.

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WALLACE LABORATORIES / *New Brunswick, N. J.*

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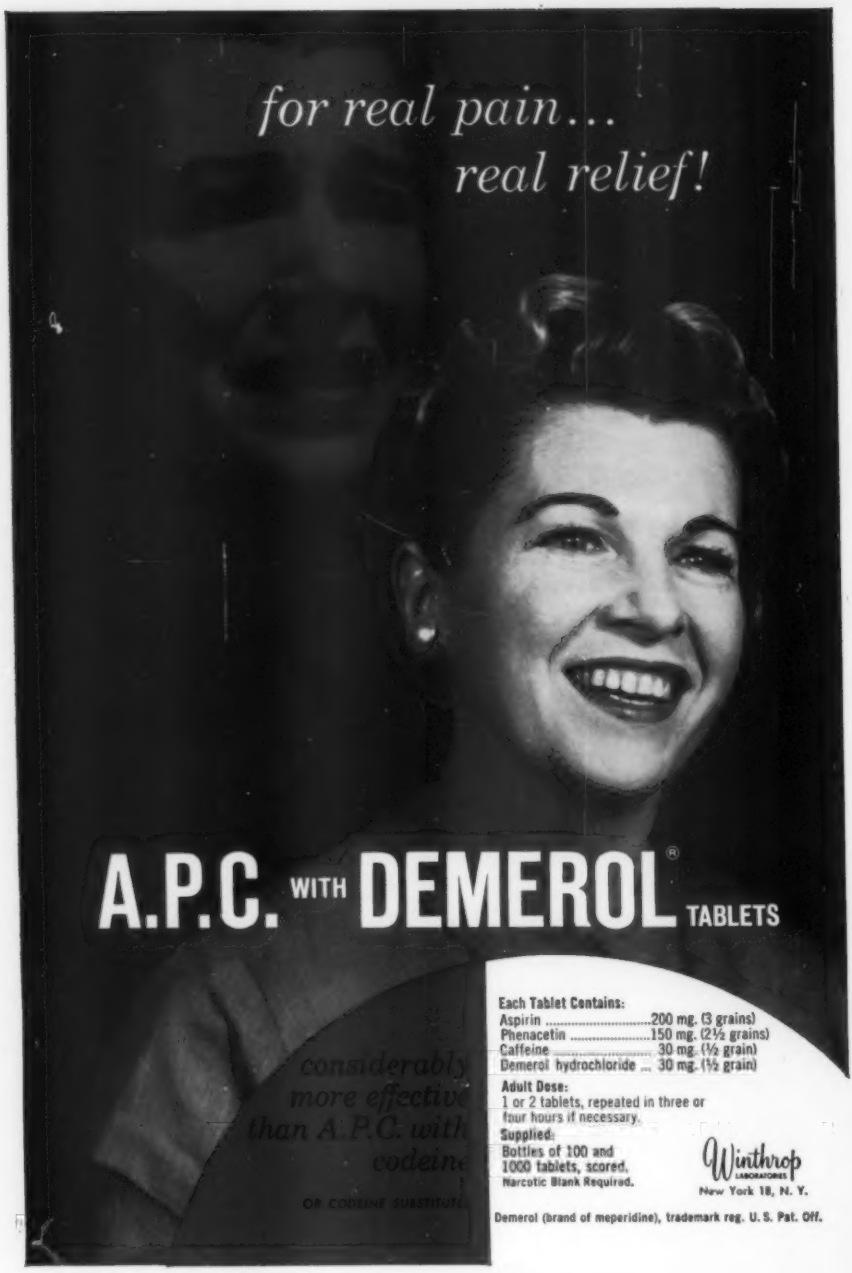
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A.P.C. WITH DEMEROL® TABLETS
considerably more effective than A.P.C. with codeine
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Each Tablet Contains:
Aspirin ..... 200 mg. (3 grains)
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Supplied:
Bottles of 100 and 1000 tablets, scored.
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